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Editorial

The Antibiotic Age

EVER since the convincing studies of Colebrook and Kenny[1] on the effectiveness of prontosil in the treatment of puerperal infections and the significant results obtained by Chain, Florey and their associates[2] following the administration of preparations of penicillin to patients with severe staphylococcal and streptococcal infections, chemotherapy and antibiotic therapy have emerged from the experimental stage; and their use in all types of infection to which man is susceptible has dominated clinical medical practice and its literature. It has been an exciting era that has seen a drop in the mortality of so serious and common a disease as pneumococcal pneumonia from 25 or 30 per cent to a probable irreducible minimum of 2 to 3 per cent; deaths from bacterial endocarditis and several forms of meningitis are reduced from 100 to 25 per cent with prospects of going lower; the management of surgical complications either threatened by or accompanying ruptured and diseased viscera is immeasurably simplified; the potentialities that were formerly contained in the possible explosion of initial local infections such as acute tonsillitis or otitis media into serious extensions of suppuration —angina, septicemia, mastoiditis, meningitis—are almost eliminated; the duration of the morbidity of innumerable non-fatal infections has been reduced in some instances to a matter of hours. Since bacterial infections of one kind or another make up such a considerable proportion of the organic ills of man, it is readily understandable that the practical uses of chemo- and antibiotic therapy should be explored to the greatest degree and that published reports of their successes and limitations should fill medical journals in the most conspicuous fashion.

That these preparations have a therapeutic value of magnificent proportions is now an established fact. It is, therefore, pertinent and of considerable interest to broaden clinical medical thought concerning antibiosis to include other phases of the subject, to consider in addition to curative effects other elements of medical importance that are developing in association with the extraordinarily widespread use of sulfonamides and penicillin, as well as newer reagents of fungal origin such as streptomycin and still others to come. It is the purpose of this article to outline some of the phases of medicine that are changing under the impact of antibiotic therapy.

One could elaborate at considerable length on the effect which this form of pan-treatment is having in substantially modifying the picture of the clinical course

[1] COLEBROOK, L. and KENNY, M. Treatment with prontosil of human puerperal infections due to haemolytic streptococci. *Lancet*, 1: 1279, 1936; *Lancet*, 2: 1319, 1936.

[2] (*a*) CHAIN, E., FLOREY, H. W., GARDNER, A. C., HEATLEY N. G., JENNINGS, M. A., ORR-EWING, J. and SANDERS, A. G. Penicillin as a chemotherapeutic. *Lancet*, 2: 226, 1940. (*b*) ABRAHAM, E. P., GARDNER, A. C., CHAIN, E., HEATLEY, N. G., FLETCHER, C. M., JENNINGS, M. A. and FLOREY, H. W. Further observations on penicillin. *Lancet*, 2: 177, 1941.

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of disease from the classical descriptions of former years, or in re-orienting points of emphasis in pathologic physiology as new aspects of disease become more apparent and relatively more significant, or in altering the morphologic pathology of inflammation in some instances and affecting the processes of repair in others. It is sufficient, however, for the purposes of this review to illustrate with a few selected examples the subject matter to which attention is invited.

As an example of the first point, namely, changing clinical pictures, pneumonia may be cited. At the present time the classical bacterial pneumonias when treated at home rarely require institutional care, and, if hospitalized, usually recover within the first twenty-four hours after admission. The greater portion of the population of protracted acute pulmonary infections is therefore now made up largely of numerous forms of suppurative and non-suppurative pneumonitis that are not amenable to antibiotic therapy. Their etiologies and pathogeneses are obscure and their clinical pictures are not well defined. For this reason they have become the most conspicuous type of acute pulmonary infections presented for discussion and study, and as a result the classical course of the rapidly cured lobar pneumonia has become for the younger generations a subject of historic interest only. This same type of change is evident in many other internal medical diseases, as well as in those encountered among the surgical and non-surgical specialties.

The veering of emphasis which has resulted from antibiotic therapy may be seen in surgical management in which patients are well saturated with antibacterial reagents before, during and after operative procedures. Since the hazards of infection are either eliminated entirely or rendered less likely, interest now centers around elements in technic that promote the maintenance of normal functional activity in spite of surgical alterations, and in minimizing the cellular and tissue damage that is an unavoidable part of surgical incisions and visceral manipulation. Factors that concern the formation of postoperative adhesions must be restudied from the point of view of the effect of antibiotic therapy on the processes of tissue repair in an abacterial surgical field.

In the field of pathology of inflammation, bacterial endocarditis may be mentioned briefly as an illustration. One of the common findings now noted at autopsy in such patients treated extensively with penicillin is either ruptured chorda tendinae or fenestrated valves. Formerly these abnormalities were rare. There is some evidence that the processes of repair in diseased valves in which the infection is either obliterated or severely restricted by penicillin are not characterized by the extensive thickening of fibrous replacement. This course of events plus the increased span of life of patients with endocarditis constitute a set of circumstances that contribute to the development of newer aspects of disorders arising from the effects of antibiotic therapy.

The discussion may be taken one step further. In viewing the antibiotic age, perhaps greater interest, even if of a more speculative nature, centers around whether or not the present day satisfaction with the success of antibacterial therapy can be transformed into a permanent optimism for generations to come. For an elaboration of this problem it is useful to consider the situation from the point of view of the bacteria themselves. These microscopic forms of viable protoplasm must be viewing with an inordinate degree of alarm the profound threat to their survival that has arisen. The situation to them is of the same magnitude as the age of the atomic bomb is to the human species.

In their common dilemma of possible annihilation, men are at the moment utilizing intellectual forces to meet the danger of extinction, while microbes are calling biologic laws into play. In the latter field, well established Darwinian principles are being invoked that determine the origin of new species and the survival of the fittest. Such processes offer to the pathogenic

bacterial species the possibility that new characteristics may emerge among strains of their population to make survival and multiplication possible in the universal antibiotic environment in which they find themselves. That events of this nature are actually happening is seen both in clinical experience in which patients are encountered whose infection is refractory to an otherwise successful form of specific treatment and in the laboratory where bacterial variants and mutants possessed of drug-resistant properties are being identified. The biologic processes involved are of immense practical clinical importance and warrant the interest of all fields of medical activity.

Although knowledge of the subject is incomplete, current information indicates that two forms of resistant strains of pathogenic micro-organisms may be encountered; the one the so-called "naturally resistant" strains, the other consisting of strains that have "acquired" resistance. A conspicuous example of the first type is found in patients who from the beginning of treatment fail to respond and from whom the strain initially isolated is found by laboratory tests to be unharmed by antibiotic substances. The second type is encountered in patients who temporarily improve under treatment and from whom cultures of the initial infecting strain are found to be susceptible to antibiotic action but who, when relapse occurs, yield cultures that are capable of multiplying in the presence of large amounts of the therapeutic reagent. The existence of naturally resistant individual strains among any bacterial species, grouped as being sensitive to antibiosis, appears to be dependent upon the fact that the cells of the particular strain have perhaps always possessed and passed on to successive generations natural properties that endowed them with this special resistance although these potentialities had never previously been realized by the bacteria nor recognized in laboratories. They represent an example of the wide variation in biologic characteristics among free-living cells based on the chance distribution of genes throughout succeeding generations. In this particular instance, by happenstance, the biologic characteristic transmitted by some gene or other defies the untoward effect of the sulfonamides, penicillin or streptomycin. The persistence of such infecting strains and the diseases which they produce are assured until some new antibiotic substance to which they are vulnerable becomes available.

Another instance of the occurrence of strains possessing initial resistance has been found in patients whose infection was derived by transmission from other patients or carriers also infected with resistant strains, in some cases of the naturally resistant type and in others created by previous treatment.

The development in patients of strains with "acquired resistance" appears to be dependent upon the classical laws of natural selection. The universal clinical practice of treating essentially all patients with specific antibacterial therapy forms ideal circumstances under which the laws of evolution and the survival of the fittest may operate. Since millions of generations of bacteria may be observed in a relatively short period of time, the elimination of the "unfit" bacteria and the retention of the drug-resistant forms is proceeding rapidly at the present time. That such a sequence of events does actually occur in disease was most clearly demonstrated in cases of gonorrhea occurring in the Armed Forces during World War II. The effective response to treatment with sulfonamides dropped in a few years time from an initially high success to a proportionately small number of cures. The failures were to a great degree directly referable to the presence in the infected population of sulfonamide-resistant strains. Fortunately, at about this time penicillin became available to meet the therapeutic problem successfully, and neisseria have not yet exhibited the capacity to resist its antibiotic action.

Still another point of special interest from a genetic and biologic point of view is found in the recent provocative reports of

Miller and Bohnoff.[3] Briefly stated, they found that among strains of meningococci some of the cells were resistant to the antibiotic effect of streptomycin. When the transfer of colonies growing on media containing streptomycin was attempted, it was found that some of them grew by subculture on other media containing streptomycin but actually failed to multiply in streptomycin-free media. Under these circumstances it appears that streptomycin, instead of being a harmful reagent, proved to be a necessary accessory nutrient factor. This finding *in vitro* was made additionally interesting by the experiments performed *in vivo* in which mice survived infection with the special strains; but if the animals were "treated" with streptomycin they died, presumably because under the latter circumstance the organisms could grow in the body more luxuriantly if streptomycin was present. In this particular experimental instance the bacteria appear to have reached the height of biologic ingenuity in that they not only did not find themselves damaged by the antibiotic reagent but utilized it for purposes of multiplication and growth. The potential implications of this circumstance for the future of antibiotic therapy are obvious. Its confirmation and further elaboration are matters of considerable importance.

There are other aspects to the problems of bacterial behavior which are of necessity omitted. A pertinent factor lies in the extent to which bacterial species are capable of utilizing the biologic laws at their disposal. They may fail. Darwin in "The Origin of the Species" has expressed this principle as follows: "Though nature grants long periods of time for the work of natural selection, she does not grant an indefinite period; for as all organic beings are striving to seize on each place in the economy of nature, if any one species does not become modified and improved in a corresponding degree with its competitors, it will be exterminated. Unless favourable variations be inherited by some at least of the offspring nothing can be effected by natural selection." It appears that this phase of the fundamental principle will have a most important bearing on the future status of the effectiveness of clinical antibiotic therapeutics.

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[3] (*a*) MILLER, C. P. and BOHNHOFF, M. Development of streptomycin-resistant variants of meningococcus. *Science*, 105: 620, 1947. (*b*) Two streptomycin-resistant variants of meningococcus. *J. Bact.*, 54: 467, 1947.

Clinical Studies

Observations on a Normal Young Woman Given Synthetic 11-Dehydrocorticosterone Acetate*

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THIS report deals with the effects of synthetically prepared 11-dehydrocorticosterone acetate (Compound A of Kendall, DHCA) in a normal female. Hitherto compounds of this type formed by the adrenal cortex have been investigated principally for their action in experimental animals and in patients with pre-existing endocrine disorders, including Addison's disease.

The possible general significance of the physiological disturbances shown by patients with Cushing's disease and allied conditions makes important any information on the action of pure compounds formed by the adrenal cortex. The demonstration by Dobriner and his associates[1] of abnormal steroids probably of adrenal origin in the urine of patients with cancer and other disorders warrants further precise study of the action of pure substances of adrenal origin.

The effects of 11-dehydrocorticosterone in animals have been reviewed by Ingle[2] and may be summarized by the statement that this substance increases working capacity, glycogenesis and sodium retention in adrenalectomized rats and prolongs their survival.

Perera, Blood and Reinhold[3] have studied the effects of 20 to 100 mg. of 11-dehydrocorticosterone acetate in two patients with Addison's disease and in one subject with hypoadrenalism secondary to anterior pituitary insufficiency. A slight retention of salt and water was observed at the higher dosage levels, whereas carbohydrate and nitrogen metabolism were not affected; no alterations were found in any of the other functions measured. Forsham, Thorn, Bergner and Emerson[4] studied the response of fourteen patients who had Addison's disease and of one normal subject to doses of 11-dehydrocorticosterone acetate varying from 10 to 60 mg. daily and concluded that "a decrease in sodium excretion occurred in 13 to 14 experiments and a decrease of chloride excretion was observed in all . . . An increased renal excretion of total nitrogen was observed in 12, of potassium in 11 and of inorganic phosphorus in 9. Uric acid excretion was increased in 13 out of 14 experiments. The percent increase in uric acid nitrogen was approximately twice as great as the increase in total nitrogen. Alpha amino acid nitrogen excretion increased significantly during Compound A therapy in the two experiments in

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† Deceased June 13, 1947.

which it was determined. During Compound A therapy fecal fat was decreased by 60% in 3 patients in whom it was studied, fecal nitrogen loss was decreased by 37% in one case with a similar decrease in wet weight. . . . In one patient 60 mg. of Compound A daily was followed by a distinctly higher glucose tolerance curve. . . . In a normal male subject maintained on a constant diet the administration of Compound A was associated with increased sodium and chloride retention. . . . There was a significant increase in urinary output of nitrogen, uric acid, potassium and inorganic phosphorus with a fall in sodium excretion." The changes on which these conclusions are based seem in many instances close to the borderline of significance.

It was also found that Compound A exerted a consistent effect in preventing hypoglycemic symptoms in patients with Addison's disease during a prolonged fast or when maintained on a low carbohydrate, high protein and high fat diet.

Sprague, Gastineau and Power[5] using 50 to 200 mg. of 11-dehydrocorticosterone acetate in a patient with Addison's disease found a mild and delayed retention of sodium chloride and water at the higher dosage level and little or no change in the glucose and insulin tolerance tests (with the exception that hypoglycemia was better tolerated). The blood sugar was better sustained during prolonged fasting when the hormone was given. Changes in the levels of the fasting blood sugar during administration of 11-dehydrocorticosterone acetate, however, were small and probably not significant. There was a moderate increase in 11-oxysteroid (cortin-like) substances in the urine while the compound was being given.

Sprague, Kepler and Power[6] studied the effects of naturally occurring 11-dehydrocorticosterone in three patients with Addison's disease and diabetes mellitus. Doses from 16 to 100 mg. were employed and the effects were studied by measuring the patient's excretion of glucose, nitrogen, ketones, sodium and chloride, and the changes in the level of the blood sugar during a twenty-four-hour fast following the withdrawal of insulin. The changes found were not impressive and may be summarized in the statement that 11-dehydrocorticosterone in the doses employed did not have a very potent effect on either electrolyte or carbohydrate metabolism in these patients.

In this communication studies are reported of several metabolic functions before, during and after the administration of 200 to 400 mg. per day of 11-dehydrocorticosterone acetate in oil to a normal woman thirty years of age. The results of this study showed that DHCA caused a mild retention of sodium and water, and had no immediate effect on the carbohydrate metabolism during forty-eight-hour fasts. There were delayed effects on the carbohydrate metabolism which could not clearly be attributed to the compound. DHCA did not change the excretion of 17-ketosteroids in the urine.

CASE REPORT

The subject used for this investigation was a white woman thirty years of age who sought medical attention six months before this reported study with complaints of premenstrual mastodynia, fatigue, nervousness and cancerophobia. She was eager to avail herself of a prolonged period of hospitalization to rule out organic disease and test the effects of certain hormones.

Physical examination was essentially negative and did not reveal any stigmata of endocrine disorder.

Routine laboratory examination including urea clearance and urine concentration and dilution tests were normal. (Table 1.)

All data indicated that the subject was physi-

cally normal but psychoneurotic and she was admitted for metabolic study. The course in the hospital was uneventful; the patient was most cooperative.

An adequate and palatable diet was composed to suit the taste of the patient and contained

During the first six days of this period the salt intake was restricted to about 2 Gm./day. Thereafter, during this period 1 ml. of normal saline solution and 1 ml. of benzyl benzoate in benzyl alcohol were administered intramuscularly on several occasions to accustom the patient

TABLE 1

BLOOD ANALYSES

Date	Hr.	Remarks	Total Protein, Falling Drop Method	Total Protein, Gm/100 ml Kjeldahl	NPN, mg/100 ml	Urea, N, mg/100 ml	Protease N, mg/100 ml	Amino N	Chlorides, mEq/liter	Na, mEq/liter	K, mEq/liter	Phosphorus Inorg. mg/100 ml	Calcium, mg/100 ml	CO_2 Combining Power, mEq/liter	Cholesterol, Tot. mg/100 ml	Blood Sugar		Uric Acid, mg/100 ml
																Date	mg/100 ml	
5.8	8 AM	Control period	7.1	6.53	24.4	....	1.1	4.23	104	139.2	4.4	2.48	11	24.8	...	5.9	98	
5.10	9 AM	.....	...	....	....	14.5	...	....	...	.....	...	....	....	....	...	5.10	124	
5.15	8 AM	.....	6.7	6.73	19.5	....	3.3	3.60	105	137.8	4.3	3.5	10.2	24.8	...	5.16	114	
5.22	8 AM	.....	6.4	6.27	22.8	....	6.6	4.88	103	137.8	4.5	3.12	10.2	25.2	...	5.17	118	
5.29	8 AM	.....	...	5.85	23.6	11.3	4.3	5.12	106	137.8	4.0	3.32	10.3	26.0	...	5.23	112	
6.6	9 AM	Fast (6.5–6.7)	...	....	21.5	7.0	3.8	4.47	105	137.8	4.4	3.62	10.5	....	...		91	3.4
6.6	3 PM	plus 11-DHCA*	...	....	15.5	5.3	1.7	4.23	108	140.6	4.4	3.46	10.5	....	...		103	3.4
6.6	9 PM	(6.5–6.10)	...	....	16.7	6.1	1.7	4.5	103	139.2	4.8	3.14	10.0	....	...		110.5	3.4
6.7	3 AM	.....	...	....	19.7	7.7	0.9	4.5	104	139.2	4.6	3.64	10.0	....	...		117.3	4.0
6.7	9 AM	.....	...	....	20	7.7	5.0	4.2	108	138.4	4.3	3.26	10.0	....	...		105	4.2
6.7	3 PM	.....	...	....	21	11.0	0	2.99	101	134.4	4.2	2.6	9.6	....	...		.....	3.6
6.11	....	Day after 11-DHCA	...	5.42	20.3	....	2.3	4.5	110	137.8	4.2	2.9	9.9	26.8	255		91	3.6
6.19	9 AM	Fast	7.3	....	20.4	7.2	1.6	3.46	111	137.8	4.2	....	....	....	...		80.5	3.6
6.19	9 PM	.....	...	....	....	6.7	...	3.35	104	137.8	7.2	3.48	10.6	....	...		80.6	3.6
6.20	9 AM	.....	...	....	20.8	8.8	8.5	4.26	104	137.8	4.3	3.38	10.4	....	...		77	4.5
6.25	9 AM	Between fasts	...	6.96	....	....	...	....	...	.....	...	....	....	....	223		149	
6.26	9 AM	.....	...	....	....	....	...	3.98	...	141	4.3	....	....	....	...		96	
6.27	8 AM	.....	7.3	6.24	....	9.1	...	....	108	140	4	2.86	10.6	24.4	...		117	3.2
7.10	9 AM	After fast	...	6.0	....	11.8	...	4.82	105	.....	...	3.2	10.1	20.4	220		93	5.4
7.18	9 AM	Before discharge	6.8	6.83	....	10.2	...	....	109	.....	...	3.1	10.3	17.2	211	7.17	117	3.8

* 11 DHCA = 11-Dehydrocorticosterone acetate.

per day carbohydrate 310 Gm.; protein 70 Gm.; fat 95 Gm.; NaCl 112 to 120 mM; total potassium 90 to 118 mM. The diet was prepared from the same stock of frozen meat and vegetables throughout the experiment and repeatedly analyzed for Na, Cl, K, N and fat. Two and a half liters of water (diet plus drinking water) were taken daily. Additional NaCl in weighed amount was given from a salt shaker as the experiment required.

The patient lived in the hospital on a fixed regimen of rest and activity, remained in bed until 10 A.M., retired at 8 P.M. and walked for two hours in the afternoon.

A preliminary period of twenty-four days was allowed during which the initial tests were done.

to injections and so avoid the subjective reactions of fear in the course of the experiment. A first forty-eight hour fast was then instituted during which only water was given. As soon as the glucose tolerance had returned to normal a second forty-eight hour fast was started and the injection of 11-dehydrocorticosterone acetate was begun.

The fast was repeated again following the return of glucose tolerance curves to normal levels and repeated once more toward the end of the experiment. Throughout the study blood was taken repeatedly for electrophoretic studies of plasma, and for determinations of the plasma volume, extracellular water and of those constituents recorded in Table 1.

Complete hematological studies were made every two or three days. The daily blood pressure readings were taken by the same physician at the same time before the patient was weighed.

DHCA administration. Daily vaginal smears were obtained following the administration.

Glucose tolerance and insulin sensitivity were measured repeatedly during the control

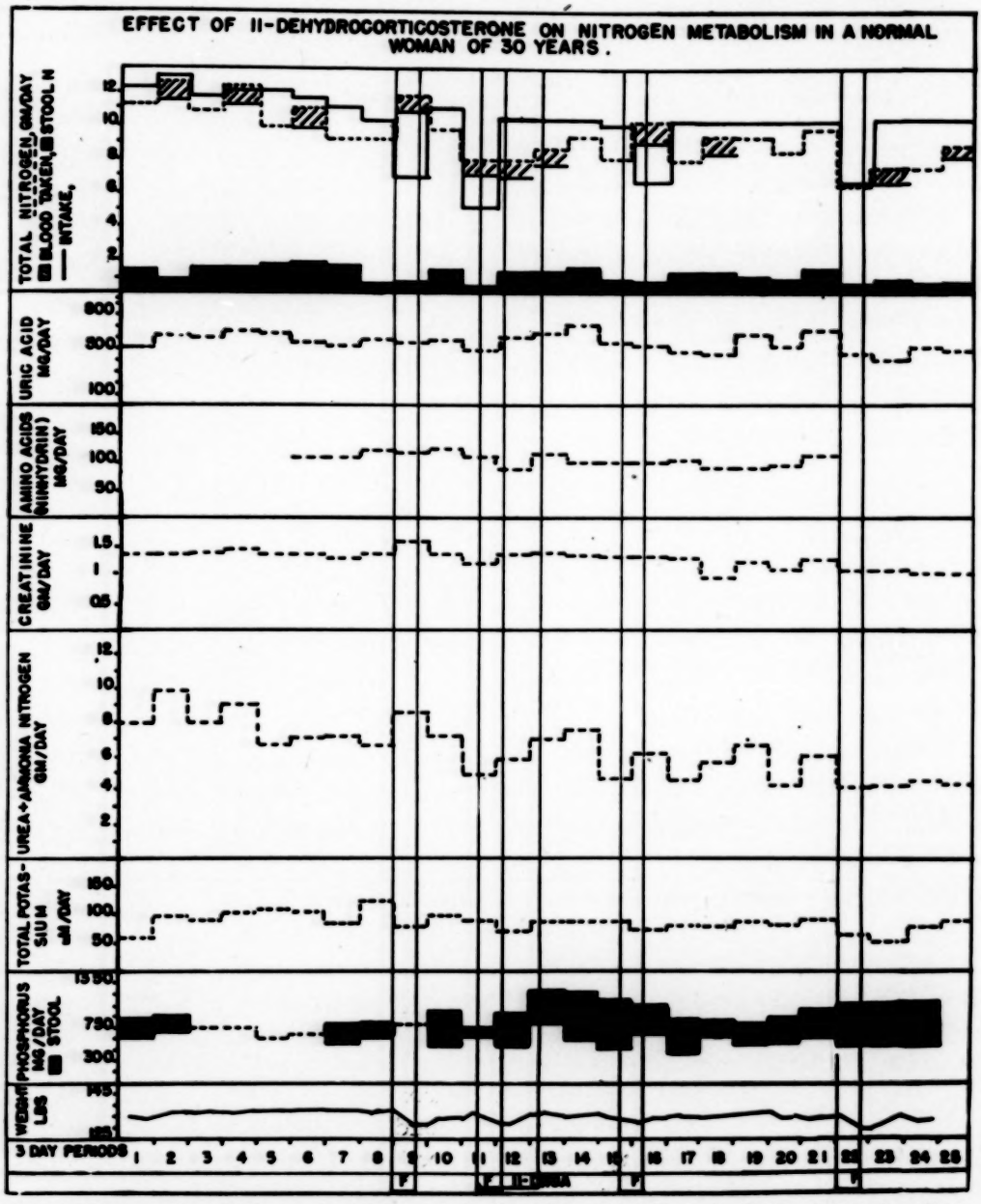

FIG. 1. Nitrogen metabolism, metabolic periods three days. Full lines signify intake, broken lines output. Vertical lines delimit fasting periods (F) and period of medication (11-DHCA). (Intake during fasting periods does not reach zero in chart because metabolic periods are seventy-two hours, fast only forty-eight hours.)

Teleroentgenograms, electrocardiograms and basal metabolic rates were obtained repeatedly before and for a period of ten days after DHCA was given and again following the period of

period and immediately after each fast on alternate days; both were repeated after each fast until they returned to normal before a new fast period was started.

The 11-dehydrocorticosterone acetate (in sesame oil, 100 mg. suspended in 1 ml.) was injected into the gluteus muscle from the thirty-second through the thirty-seventh day of the experiment. Half of the daily dose was given in the morning, the other half seven hours later. The amounts administered were: on the thirty-second day 200 mg., the thirty-third day 400 mg., from the thirty-fourth day through the thirty-seventh day 200 mg. daily. The total amount given was 1,400 mg.

Stools were collected in three-day specimens. Charcoal was used as a marker. Urines were collected daily in twenty-four hour samples. During the fasting periods urines were collected in twelve-hour periods. Acetic acid was used to preserve the urines after the aliquot for 17-ketosteroid determination had been removed; no preservative was used for the stools. All excreta were kept in the refrigerator during collection.

Standard methods described by Peters and Van Slyke[7] were used for all determinations of chemical blood constituents recorded in Table I and for the determination of all constituents in urine and feces except for those specifically mentioned below. Potassium and sodium in blood, urine and feces were measured by flame photometry;[8] in the case of the fecal material following dry ashing in a muffle furnace at 500°c. Fecal fat was determined using the wet combustion method.[7] Amino nitrogen in the blood and urine was measured by the ninhydrin method.[9] Urinary 17-ketosteroids were measured by the method of Callow[10] and the modification of Talbot.[11]

Glucose tolerance tests were done as described by Thorn[12] with chemical measurements by the technic of Somogyi, Hartmann and Shaffer.[13] Insulin sensitivity was measured by determining the blood sugar by the above method every one-half hour for three hours after the intravenous injection of 0.1 unit of insulin per Kg. (U.S.P.). Plasma volume was measured by the use of Evans blue[14] and extracellular water was measured by the use of sodium thiocyanate.[15] The technic employed for the electrophoretic analysis of plasma proteins has been described in detail by Peterman et al.[16]

TABLE II
DAILY NITROGEN BALANCE
GM./DAY

Date	Urine	Stool	Total Output	Total Intake	Balance
1946					
May 5–6	6.23				
6–7	8.83	1.26	10.09		
7–8	12.17	1.26	13.43	12.66	− .77
8–9	11.19	1.26	12.45	12.66	*−2.85
9–10	11.70	.75	12.45	12.66	+ .21
10–11	9.00	.75	9.75	12.66	*+2.61
11–12	10.47	.75	11.22	12.66	+1.44
12–13	9.54	1.31	10.85	10.83	− .02
13–14	8.47	1.31	9.78	10.83	+1.05
14–15	9.20	1.31	10.51	12.66	+2.15
15–16	9.76	1.44	11.20	12.66	*−1.69
16–17	10.54	1.44	11.98	10.83	−1.15
17–18	8.81	1.44	10.25	10.83	+ .58
18–19	8.54	1.51	10.05	12.66	+2.61
19–20	7.63	1.51	9.14	10.69	+1.55
20–21	5.46	1.51	6.97	12.66	+5.69
21–22	11.35	1.54	12.89	10.83	−2.06
22–23	8.20	1.54	9.74	12.66	* −.21
23–24	4.01	1.54	5.55	10.80	−5.25
24–25	10.43	1.44	11.87	12.50	+ .63
25–26	7.77	1.44	9.21	10.83	+1.62
26–27	9.32	1.44	10.76	12.66	+1.90
27–28	6.86	.68	7.54	10.83	+3.29
28–29	8.27	.68	8.95	12.66	+3.71
29–30	11.20	.68	11.88	6.90	*−8.13
30–31	7.73	.75	8.45	.....	−8.45
31–1	11.25	.75	12.00	7.15	−4.85
June 1–2	9.03	.75	9.78	12.66	+2.88
2–3	7.92	1.37	9.29	10.83	+1.54
3–4	8.12	1.37	9.49	12.61	+3.12
4–5	7.68	1.37	9.05	10.83	+1.78
5–6	6.75	.36	7.11	7.94	+ .83
6–7	5.53	.36	5.89	.....	*−7.05
7–8	6.79	.36	7.15	7.15	*−3.60
8–9	6.58	1.05	7.63	10.98	+3.35
9–10	7.46	1.05	8.51	12.80	+4.29
10–11	7.89	1.05	8.94	10.94	+2.00
10–12	7.15	1.07	8.22	12.78	*+1.41
12–13	7.61	1.07	8.68	10.94	+2.26
13–14	4.69	1.07	5.76	12.80	+7.04
14–15	10.53	1.29	11.82	10.98	− .84
15–16	9.30	1.29	10.59	12.80	+2.21
16–17	6.28	1.29	7.57	10.98	+3.41
17–18	8.12	.99	9.11	12.74	+3.63
18–19	6.78	.99	7.77	6.43	−1.34
19–20	6.39	.99	7.38	0	*−9.78
20–21	9.50	.80	10.30	5.85	*−7.00
21–22	8.50	.80	9.30	11.20	+1.90
22–23	7.82	.80	8.62	9.28	+0.66
23–24	6.37	1.04	7.41	11.20	+3.79
24–25	6.48	1.04	7.52	9.28	+1.76
25–26	5.80	1.04	6.84	11.20	+4.36
26–27	9.97	1.11	11.08	9.28	*−2.40
27–28	2.18	1.11	3.29	11.20	*+5.26
28–29	11.09	1.11	12.20	9.28	−2.92
29–30	7.50	.96	8.46	11.20	+2.74
30–1	6.70	.96	7.66	9.28	+1.62

TABLE II (*Continued*)

Date	Urine	Stool	Total Output	Total Intake	Balance
July 1–2	7.27	.96	8.23	11.20	+2.97
2–3	8.28	.70	8.98	9.28	+0.30
3–4	6.75	.70	7.45	11.20	+3.75
4–5	9.18	.70	9.88	9.28	−0.60
5–6	8.53	1.22	9.75	11.20	+1.45
6–7	7.83	1.22	9.05	9.28	+0.23
7–8	8.85	1.22	10.07	11.20	+1.13
8–9	6.26	.44	6.70	5.70	−1.00
9–10	3.36	.44	3.80	.....	−3.80
10–11	9.04	.44	9.48	5.85	−3.63
11–12	7.30	.79	8.09	11.20	+3.11
12–13	6.70	.79	7.49	9.28	+1.79
13–14	4.60	.79	5.39	11.20	+5.81
14–15	8.32	.56	8.88	9.28	+0.40
15–16	7.74	.56	8.30	11.20	+2.90
16–17	7.58	.56	8.14	9.28	+1.14
17–18	6.90	....	.....	11.20	

* Nitrogen withdrawn by bleeding included in balance figure.

RESULTS

Throughout the experiment except during periods of fasting the nitrogen balance remained slightly positive. (Fig. 1 and Tables II and III.) No significant effects were noted after the administration of the DHCA. In the more detailed studies of the fasting periods (Fig. 2), it appears that the rise of nitrogen excretion during the end of and following the fasting period was somewhat slower while the compound was administered than it had been in the control fasting periods and before twenty-eight days following DHCA administration. A similar lag of nitrogen excretion behind normal levels was seen in the fasting period five days after the hormone was given. The amino nitrogen excretion during the four fasting periods was essentially unchanged. Blood amino nitrogen fell to a low level at the end of the fast period during which DHCA was given (2.99 mg./100 ml.), whereas the values remained high during the other two fasts after the DHCA injections (4.26 and 4.82 mg./100 ml.). No significant changes in serum phosphorus, proteoses, blood urea and non-protein nitrogen or serum potassium occurred. (Table I.)

Electrophoretic studies of the plasma proteins at various times during the study showed variations which could not be correlated with any known factors and which were within the ex-

TABLE III

URINARY NITROGEN FRACTIONS AND MINERALS EXCERTED IN 24 HOURS

Date	Urea Nitrogen, Gm/Day	Uric Acid, mg/Day	Creatinine, mg/Day	Amino Nitrogen, mg/Day	Sodium, mM/Day	Potassium, mM/Day	Phosphate, mg/Day
1946							
May 5–6	6.6	271	795		95.2	24.2	557
6–7	9.1	572	1230		102.5	38.2	444
7–8	7.5	690	1968		100.4	106.1	858
8–9	10.6	694	1434		40.6	103.51	671
9–10	10.0	697	1360		22.4	88.5	793
10–11	* 9.1	602	1421		12.8	83.3	695
11–12	8.7	553	1360		15.04	90.0	787
12–13	7.8	642	1320		88.0	85.5	711
13–14	6.66	578	1380		149.0	90.0	691
14–15	9.40	677	1599		123.0	108.0	728
15–16	8.34	705	1353		84.6	104.0	767
16–17	8.97	693	1414		84.6	83.0	738
17–18	5.77	609	1301		122.0	100.0	528
18–19	6.87	619	1380		87.0	114.8	663
19–20	6.46	492	1260		79.5	85.5	605
20–21	4.81	420	960	76	72.0	81.0	348
21–22	9.04	770	1860	140	96.0	128.3	977
22–23	6.92	624	1360	111	75.0	91.5	635
23–24	3.33	283	680	44	68.0	60.0	239
24–25	10.57	715	1800	123	160.5	92.2	785
25–26	7.50	574	1320	103	126.0	92.2	493
26–27	9.37	657	1560	126	114.0	128.0	781
27–28	5.13	508	1080	100	84.0	90.0	309
28–29	4.74	633	1440	116	132.0	137.0	736
29–30	9.08	816	1980	111	112.5	117.0	1016
30–31	6.05	393	1530	111	50.5	44.3	769
31–1	10.0	492	1300	106	81.5	54.0	1228
June 1–2	6.62	658	1280	118	42.8	90.0	518
2–3	7.87	597	1260	131	129.0	90.0	388
3–4	6.83	522	1560	127	112.5	101.2	593
4–5	5.90	554	1260	115	96.0	101.2	621
5–6	4.64	475	1360	84	62.4	91.5	723
6–7	3.78	385	960	83	33.6	45.6	573
7–8	5.64	583	1390	90	15.6	41.2	629
8–9	5.37	634	1280	110	8.0	64.5	420
9–10	6.68	586	1400	119	30.0	87.0	491
10–11	6.84	625	1240	102	56.0	69.0	518
11–12	7.44	669	1360	115	155.0	90.0	1273
12–13	6.32	649	1586	119	118.95	84.64	620
13–14	5.06	673	920	115*	110.0	67.5	282
14–15	8.29	765	1620	115*	129.0	90.0	797
15–16	7.81	694	1400	115*	161.0	90.0	781
16–17	4.63	514	960	113	119.0	70.5	420
17–18	4.48	623	1440	116	129.0	94.5	434
18–19	4.62	540	1200	111	53.0	60.0	570
19–20	4.63	477	1270	70	60.55	48.4	734
20–21	7.99	557	1320	73	38.4	39.9	719
21–22	6.12	524	1360	105	56.0	78.0	540
22–23	4.48	447	1380	129	75.0	74.2	302
23–24	3.58	408	1160	111	107.0	82.5	471
24–25	5.45	565	1360	94	97.0	67.5	540
25–26	4.81	333	540	110*	71.0	63.8	245
26–27	8.71	803	1720	110*	117.0	85.5	885
27–28	2.16	275	540	110*	40.0	63.75	229
28–29	8.61	716	1480	110*	112.0	90.0	794
29–30	5.95	661	1200	110*	129.0	70.5	508
30–1	4.94	539	1020	110*	129.0	83.25	410
July 1–2	4.71	550	1200	110*	99.0	88.7	583
2–3	5.43	580	1160	110*	99.0	75.0	583
3–4	2.94	400	920	110*	86.0	67.5	470
4–5	6.62	669	1380	110*	109.5	85.5	705
5–6	5.59	604	1200	119	106.0	89.0	622
6–7	5.88	646	1200	104	116.0	84.0	590
7–8	6.47	696	1440	118	136.0	101.0	705
8–9	4.41	430	1080	52	66.0	63.0	515
9–10	2.32	286	816	37	34.4	48.3	296.6
10–11	6.58	503	1130	92	78.0	32.0	595
11–12	5.66	527	1240	113	17.0	64.0	423
12–13	4.41	497	720	90	72.0	66.0	477
13–14	3.56	301	720	66	144.0	65.0	327
14–15	5.44	575	1160	99	124.0	74.0	591
15–16	5.44	586	1240	556	130.0	63.0	508
16–17	5.0	844	1080	622	92.0	77.0	610
17–18	3.97	...	1120	561	116.0	68.0	514

* Represents pooled collections.

perimental errors involved in the determination of plasma volumes and of plasma protein concentration. (Table IV.)

Except for the initial period of salt depletion, three periods were noted (Fig. 3) during which not parallel variations in humidity or temperature and might be of significance. A trend in the same direction but far less conclusive was noted in the urine excretion of sodium. (Fig. 3, Table III.) While there were no significant changes in

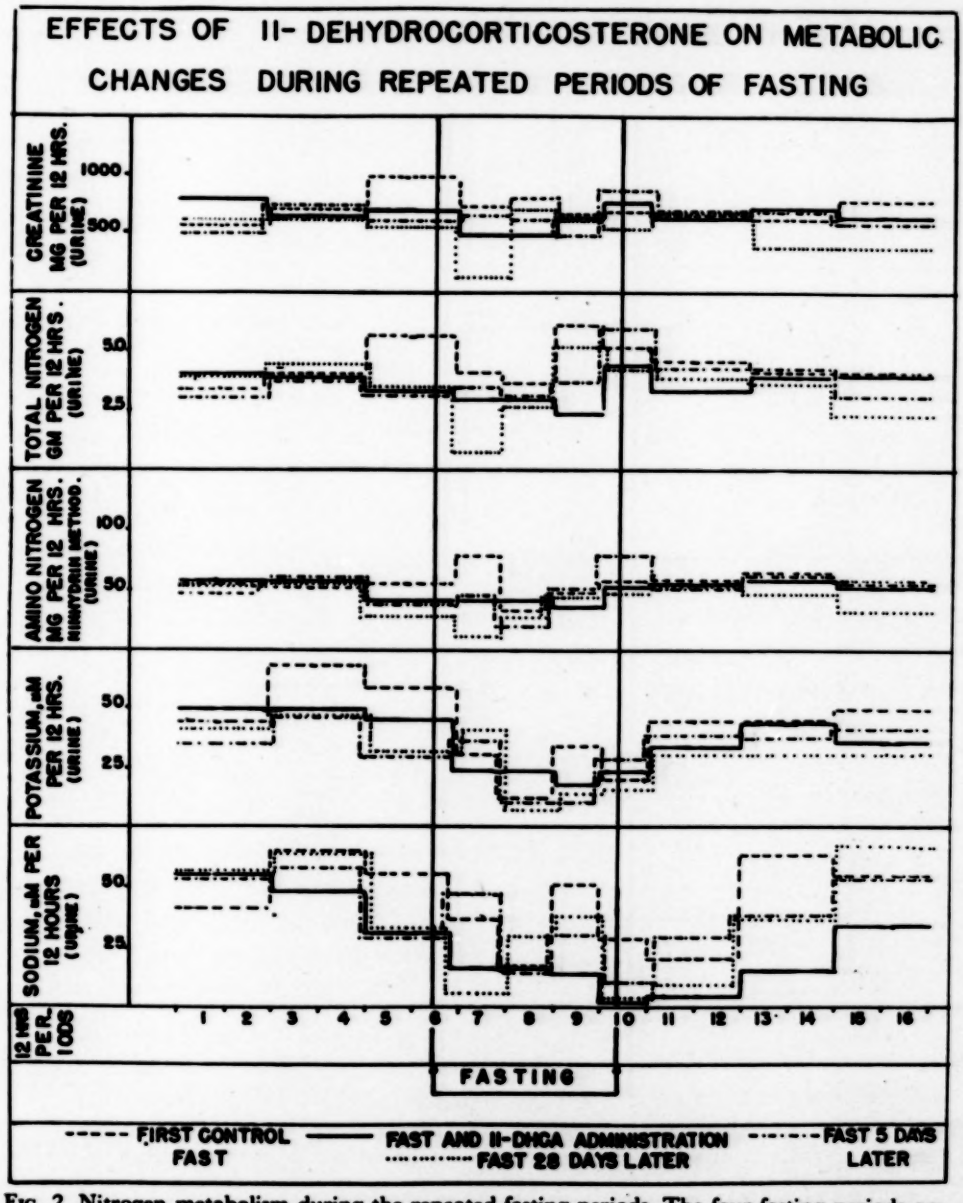
EFFECTS OF 11- DEHYDROCORTICOSTERONE ON METABOLIC CHANGES DURING REPEATED PERIODS OF FASTING
CREATININE MG PER 12 HRS. (URINE)
1000
500
TOTAL NITROGEN GM PER 12 HRS. (URINE)
5.0
2.5
AMINO NITROGEN MG PER 12 HRS. NINHYDRIN METHOD. (URINE)
100
50
POTASSIUM, mM PER 12 HRS. (URINE)
50
25
SODIUM, mM PER 12 HOURS (URINE)
50
25
12 HR PERIODS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
FASTING
FIRST CONTROL FAST
FAST AND 11-DHCA ADMINISTRATION
FAST 28 DAYS LATER
FAST 5 DAYS LATER

FIG. 2. Nitrogen metabolism during the repeated fasting periods. The four fasting periods are superimposed upon each other on a single time scale.

the urine volume gradually decreased (periods 7 to 10, 15 to 18, and 21 to 22). The first and the last of these occurred before menstruation. The one extending from the fifteenth to the eighteenth metabolic period followed the administration of the DHCA. These changes did the serum concentration of potassium and phosphorus a slight increase of sodium (from 137.8 to 141 mEq./l.) occurred sixteen days after the last injection of the DHCA. This coincided with the lowered urinary excretion of this ion.

During the control period three glucose

tolerance curves were obtained which closely corresponded. (Fig. 4, Table v.) This was also true of three insulin sensitivity tests.

After a forty-eight-hour fast without medication the glucose tolerance was decreased. It after three days (somewhat more rapidly). During this test the blood sugar values, 91 to 117 mg./100 ml., were within the normal range. The insulin sensitivity curves were essentially those obtained during the control period.

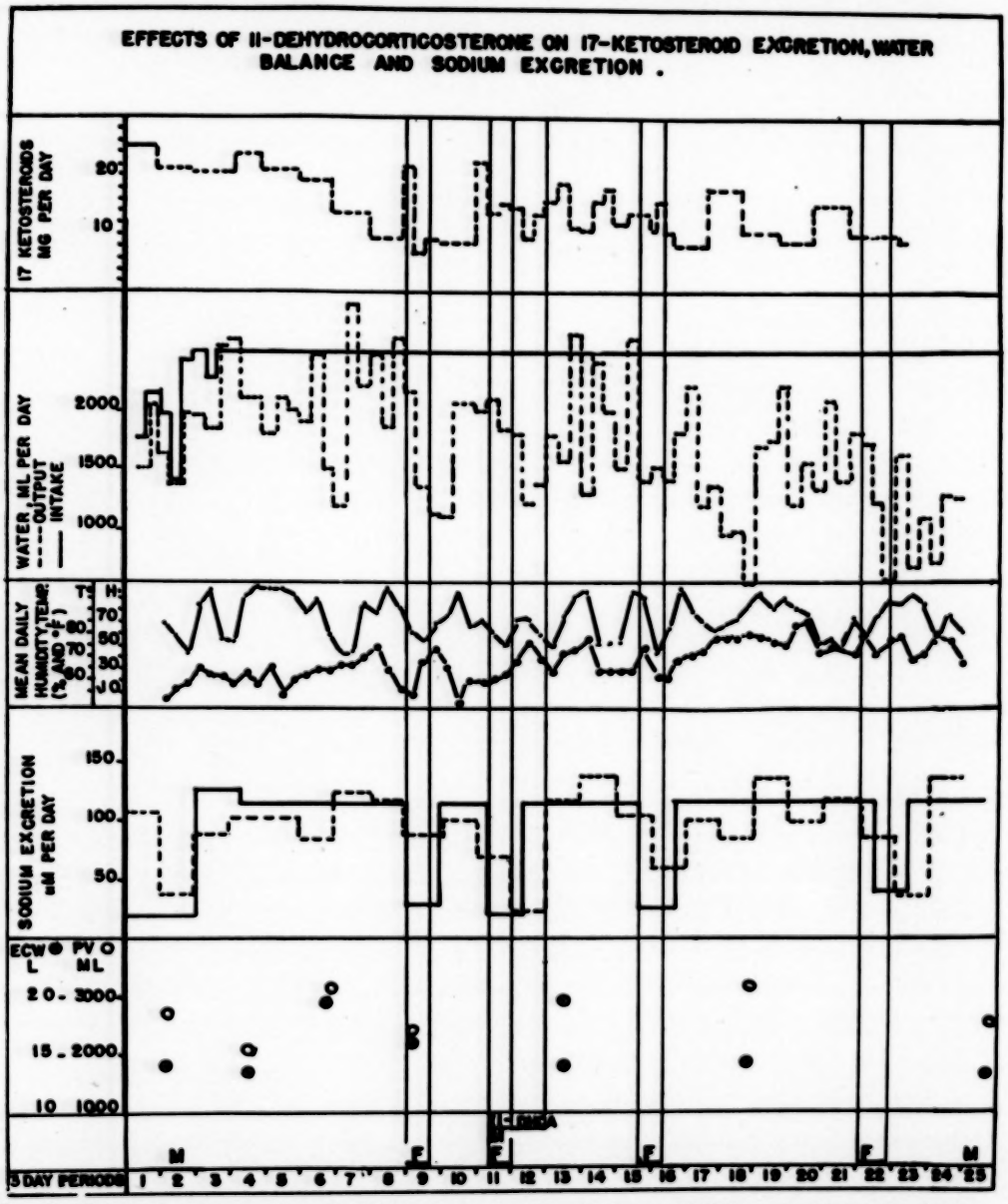
EFFECTS OF 11-DEHYDROCORTICOSTERONE ON 17-KETOSTEROID EXCRETION, WATER BALANCE AND SODIUM EXCRETION .
17 KETOSTEROIDS MG PER DAY
WATER, ML PER DAY
OUTPUT
INTAKE
MEAN DAILY HUMIDITY (%) AND TEMP. (°F)
SODIUM EXCRETION mM PER DAY
ECW @ L
PV O ML
11-DHCA
3 DAY PERIODS

FIG. 3. 17-ketosteroid excretion, fluid balance and sodium balance. Full lines signify intake, broken lines output; metabolic periods three days. Vertical lines delimit fasting periods (F) and period of medication (11-DHCA). M signifies onset of menstruation.

returned to normal within six days after the standard diet had been resumed. Insulin sensitivity was not tested at this point.

After a forty-eight-hour fast during which the hormone was injected, the glucose tolerance was similarly decreased but approached normal

After the third forty-eight-hour fast, ten days following the last injection of 11-dehydrocorticosterone acetate, the glucose tolerance curve was markedly changed. It was flattened with a lower peak. The initial fasting blood sugar was depressed to 80.5 mg./100 ml., and the insulin

sensitivity was decreased (maximal blood sugar fall from 80 to 60 mg./100 ml.). During this fast the blood sugar was low and averaged 77.5 mg./100 ml. Two days later glucose tolerance was decreased, as compared with the normal, and identical with that previously found

TABLE IV
TOTAL CIRCULATING PLASMA PROTEINS

Date	Plasma Volume	Total Protein	Albumin	α_1	α_2	β	ϕ	γ
5–8	2860	187	100	10	17	28	9	22
5–15	2080	140	74	9	14	20	7	16
5–22	3060	192						
5–29	2260	132	64	10	14	22	9	14
6–11	2920	158	81	12	15	25	9	17
6–27	3160	197	101	14	19	33	8	23
7–18	2520	172						

immediately after the forty-eight-hour fasts. This abnormality persisted for eight days after the fast and the insulin sensitivity curves returned to normal nine days after the fasting period.

Twenty-eight days after the last injection of the DHCA the measurements of glucose tolerance and insulin sensitivity were repeated. The slope of the first glucose tolerance curve taken after the fasting was still flat, as it had been after the control fasting period, but the peak of the curve remained within the normal range. Two days later the curve tended to return towards normal and finally became so four days later. Only one fasting blood sugar, obtained six days after the fast, was low (84 mg./100 ml.).

There had been mild reactions to the insulin sensitivity tests in the control period and during the fast when no medication was given; none occurred after the injection of 11-dehydrocorticosterone acetate. One severe "shock-like" reaction occurred during a glucose tolerance test on the fifth day after the fast during hormone administration when the blood sugar level was 70 mg./100 ml.

No ketone bodies were found in the urine during any of the fasts. Glucose was not measured in the urine during the glucose tolerance tests.

TABLE V
FASTING BLOOD SUGAR VALUES

Date	Remarks	Fasting Blood Sugar, mg/100 ml.
5.9	Control Period	98
5.10	.....	124
5.16	.....	114
5.17	.....	118
5.23	.....	112
5.24	.....	114
	Average of Control Period	... 113.3
	Range	... 98–124
5.31	After 48 hours fast	107
6.3	.....	113
6.5	.....	114
	Average after fast	... 111.3
	Range	... 107–114
6.6 9 AM	During fast—11-DHCA*	91
3 PM	.....	103
9 PM	.....	110.5
6.7 3 AM	.....	117.3
9 AM	.....	105
	Average during fast—11-DHCA	... 105.4
	Range	... 91–117
6.10	After fast—11-DHCA	105
6.11	.....	91
6.12	.....	110
6.17	.....	109
	Average after fast—11-DHCA	... 103.7
	Range	... 91–109
6.19 9 AM	During fast 10 days after 11-DHCA	80.5
9 PM	.....	80.6
6.20 9 AM	.....	77
1 PM	.....	72
	Average during fast 10 days after 11-DHCA	... 77.5
	Range	... 72–80.6
6.21	After fast 12 days after 11-DHCA	82
6.22	.....	91
6.25	.....	149
6.26	.....	96
6.27	.....	117
6.28	.....	89
6.29	.....	117
7.2	.....	103
	Average after fast 12 to 22 days after 11-DHCA	... 108.8
	Range	... 82–149
7.8	After last fast 28 days after 11-DHCA	107
7.10	.....	93
7.11	.....	105
7.12	.....	117
7.15	.....	84
7.16	.....	117
7.17	.....	117
	Average after last fast	... 105.5
	Range	... 84–117

* 11-DHCA = 11-dehydrocorticosterone acetate.

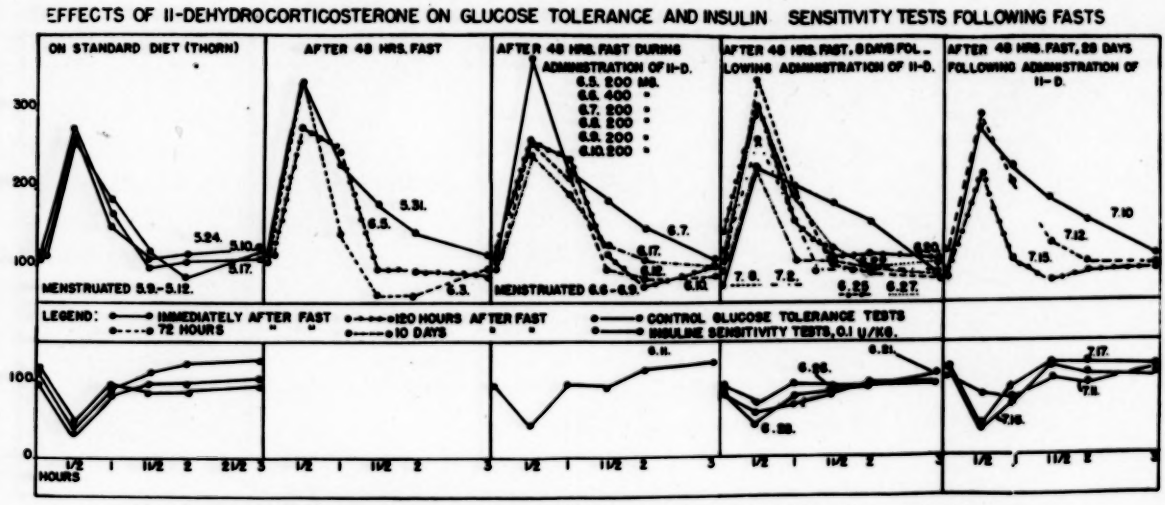
EFFECTS OF 11-DEHYDROCORTICOSTERONE ON GLUCOSE TOLERANCE AND INSULIN SENSITIVITY TESTS FOLLOWING FASTS
ON STANDARD DIET (THORN)
AFTER 48 HRS. FAST
AFTER 48 HRS. FAST DURING ADMINISTRATION OF 11-D.
AFTER 48 HRS. FAST, 8 DAYS FOLLOWING ADMINISTRATION OF 11-D.
AFTER 48 HRS. FAST, 28 DAYS FOLLOWING ADMINISTRATION OF 11-D.
MENSTRUATED 5.9.-5.12.
LEGEND: IMMEDIATELY AFTER FAST
72 HOURS
120 HOURS AFTER FAST
10 DAYS
CONTROL GLUCOSE TOLERANCE TESTS
INSULINE SENSITIVITY TESTS, 0.1 U/KG.
HOURS

FIG. 4. Carbohydrate metabolism; repeated glucose tolerance and insulin sensitivity tests.

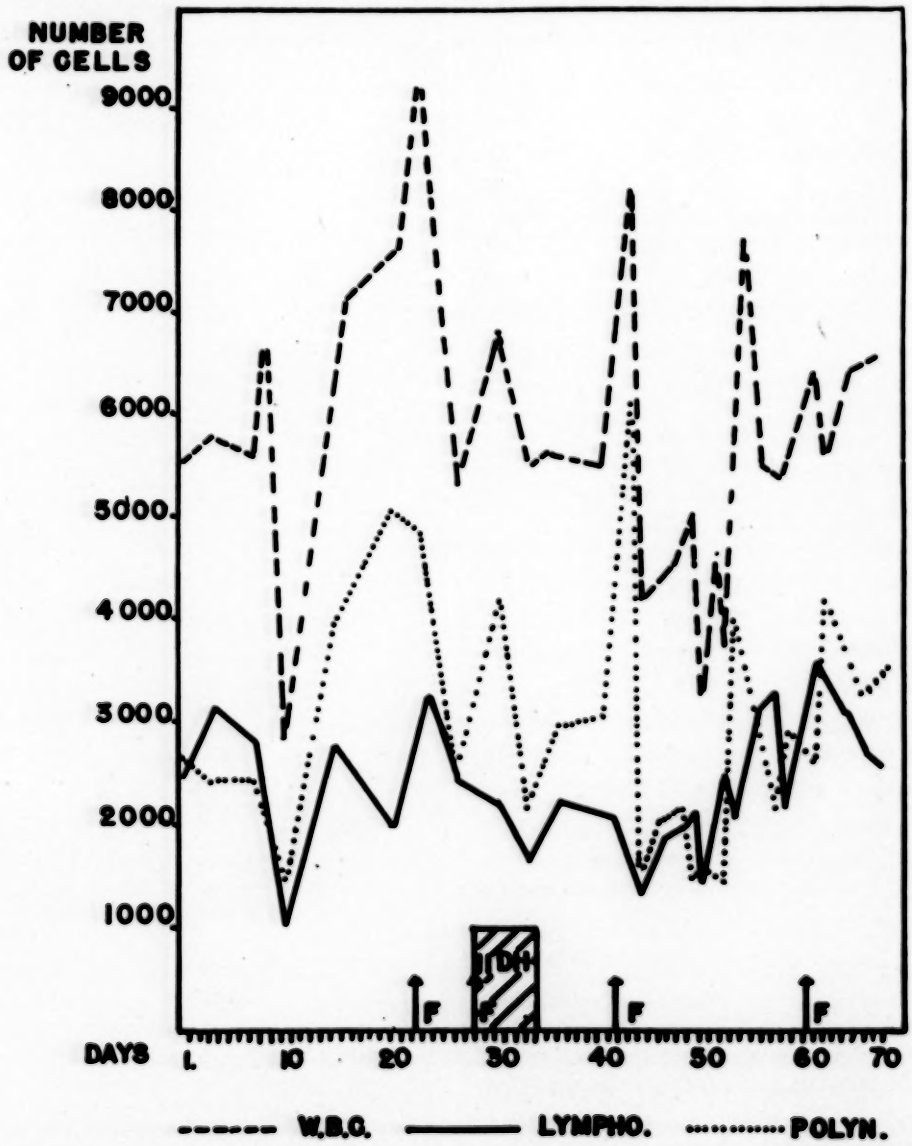

FIG. 5. Leukocytosis in cells/c.mm. showing considerable daily variation and the absence of any consistent change following administration of 11-DHCA.

The fecal excretion of nitrogen diminished by 50 per cent just before the administration of DHCA so that the later return of fecal nitrogen to premedication levels is probably unrelated to DHCA. Phosphorus increased considerably in the feces following the DHCA injection but a similar rise was again seen toward the end of the experiment. The total fat in the feces decreased by 50 per cent during the three days following injection of 11-dehydrocorticosterone acetate to a level of 2.5 Gm./day in the following three day period. Such changes, however, frequently occur in the absence of any medication.

Because of the observations of Dougherty and White[17] and of de la Balze, Reifenstein and Albright[18] blood counts were followed throughout the study. As charted in Figure 5 the variations were considerable but no consistent change followed administration of DHCA.

No significant changes of extracellular water or plasma volume occurred. The basal metabolic rate, electrocardiogram and teleroentgenograms remained normal at all times. A slight and progressive drop of the urinary 17-ketosteroid excretion was not changed by the administration of the hormone. Following the administration of DHCA the patient complained of nausea for two weeks; there were no other subjective changes.

Findings on urinary gonadotropins, results of steroid fractionations and vaginal smears will be reported elsewhere.

COMMENTS

Since the excretion of nitrogen during the periods of fasting with and without administration of 11-dehydrocorticosterone acetate remained essentially the same this compound in the dosage employed apparently exerted no gluconeogenic effects measurable by the methods employed. Likewise, the behavior of the glucose tolerance and insulin sensitivity remained unchanged during the administration of the compound. It seemed at first that ten days after the last injection of DHCA changes in carbohydrate metabolism occurred, blood sugar levels fell and glucose tolerance increased after fasting; however, a few days later glucose tolerance decreased whereas insulin sensitivity remained impaired. Twenty-eight days after the last injection of the compound the glucose tolerance after fasting was still not exactly that which was obtained after the control fast; hence, these changes could not be definitely ascribed to the DHCA. It does appear possible, nevertheless, that there may be following the administration of an oil suspension of 11-dehydrocorticosterone acetate delayed effects manifested only by the changes in carbohydrate metabolism since all other functions studied remained unchanged or were merely questionably altered.

There was mild sodium retention while the compound was being given, associated with a decreased urine volume. The rise of sodium concentration in the serum coincident with the retention of the ion, however, was insignificant (1.7 per cent).

Possibly, oil suspensions of this compound are absorbed very slowly and studies of their effects may have to be continued far beyond the period of administration of the material. Furthermore, large doses may be needed to produce measurable physiological results. One cannot exclude the possibility that the changes observed were incidental to the repeated periods of fasting, or that they may represent the result of a hormonal imbalance produced by the compound injected rather than direct effects of 11-dehydrocorticosterone acetate itself. Finally, DHCA may have metabolic properties which can be demonstrated readily during anabolism but only with difficulty during fasting.

CONCLUSIONS AND SUMMARY

1. A dosage of 200 to 400 mg. per day of synthetic 11-dehydrocorticosterone acetate (DHCA), a total dose of 1,400 mg., failed to alter the immediate metabolic response to repeated forty-eight-hour fasts in a normal woman.

2. Delayed changes in the response of carbohydrate metabolism to a forty-eight-hour fast ten days after the last injection of DHCA are difficult to interpret and cannot clearly be attributed to 11-dehydrocorticosterone acetate.

3. There was mild retention of sodium and water following the administration of 11-dehydrocorticosterone acetate.

4. The 17-ketosteroid excretion was not increased following injection of 1,400 mg. of 11-dehydrocorticosterone acetate.

The synthetic 11-dehydrocorticosterone acetate used in this study was kindly supplied by Merck and Co., Rahway, N.J. The electrophoresis studies were conducted by Dr. M. L. Petermann, the 17-ketosteroid studies by Dr. K. Dobriner and studies of vaginal smears were made in Dr. E. Shorr's laboratory by Dr. A. C. Carter. The assistance of Dr. E. C. Reifenstein, Jr. in the preparation of the manuscript is gratefully acknowledged.

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Effects of Synthetic 11-Dehydrocorticosterone (Compound A) in a Subject with Addison's Disease*†

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THE recent synthesis of 11-dehydrocorticosterone (compound A of Kendall) on a large scale brought with it the hope that this steroid would provide an improved form of treatment for Addison's disease, mainly because the naturally occurring compound had been shown in animal experiments to have effects on the metabolism of both carbohydrate and electrolytes. The only synthetic steroid which has heretofore been generally available for the treatment of Addison's disease, namely, 11-desoxycorticosterone acetate, has profound effects on electrolyte metabolism but is almost totally lacking in carbohydrate activity. Perhaps in part because of this lack, 11-desoxycorticosterone acetate has serious shortcomings in the treatment of chronic adrenal insufficiency. There was reason, therefore, to hope that 11-dehydrocorticosterone might prove to be an important addition to the therapy of this condition.

Reports of the action of synthetic 11-dehydrocorticosterone acetate in cases of adrenal cortical insufficiency in human beings have been made by Forsham, Thorn, Bergner and Emerson and by Perera, Blood and Reinhold. The former investigators studied its effects during short periods in doses varying between 10 and 60 mg. daily in fourteen patients with Addison's disease; the latter investigators studied its effects in doses varying between 20 and 100 mg. daily in two patients with Addison's disease and in one with adrenal cortical insufficiency secondary to anterior pituitary insufficiency. Both groups of investigators observed that the compound induced retention of sodium chloride and water but that it was relatively deficient in this action as compared to 11-desoxycorticosterone acetate. Forsham, Thorn, Bergner and Emerson reported possible effects of the compound on carbohydrate metabolism in the form of a higher glucose tolerance curve in one patient out of three, a greater fall in serum inorganic phosphorus in two patients out of three during glucose tolerance tests which were done during treatment with 11-dehydrocorticosterone acetate and a consistent effect in preventing symptoms of hypoglycemia in patients with Addison's disease during prolonged fasting and during periods on a low carbohydrate diet. An increased excretion of nitrogen in the urine, 1.2 Gm. per day, was observed in twelve experiments out of fourteen. Perera, Blood and Reinhold, on the other hand, noted no effects on carbohydrate metabolism as measured by fasting respiratory quotients and intravenous glucose tolerance tests. Their patients were

* From the Mayo Clinic, Rochester, Minn.

† The dehydrocorticosterone and dehydrocorticosterone acetate used in this study were kindly supplied by Merck and Company, Inc., Rahway, N. J.

not subjected to the stress of prolonged fasting. However, symptoms of hypoglycemia, at one time associated with a blood sugar level of 57 mg. per 100 cc., were observed in one patient on several occasions when he was receiving 40 mg. of 11-dehydrocorticosterone acetate daily. No definite or consistent effect on nitrogen excretion was observed.

Homburger, Abels, Young and Rhoads observed the effects of 11-dehydrocorticosterone acetate in doses of 200 to 400 mg. per day, totaling 1,400 mg., in a normal young woman. Mild retention of sodium and water followed administration of the hormone but there were no changes in carbohydrate metabolism which could clearly be attributed to the hormone.

Sprague, Kepler, Keating and Power administered naturally occurring 11-dehydrocorticosterone and 17-hydroxy-11-dehydrocorticosterone to three patients with coexisting Addison's disease and diabetes who consented to act as subjects. The effects of the compounds were measured by means of determinations of the blood sugar and urinary glucose, nitrogen and ketone bodies during fasting after withdrawal of insulin. In only one of the three cases did 11-dehydrocorticosterone in doses of 16 to 50 mg. daily intensify the diabetes appreciably; 17-hydroxy-11-dehydrocorticosterone, on the other hand, in doses of 8 to 20 mg. daily, produced marked intensification of the diabetes in two cases and slight intensification in the third case.

The foregoing studies seem to indicate that 11-dehydrocorticosterone acetate has some effect in inducing retention of salt and water in the human subject but that it is relatively deficient in carbohydrate activity in the doses employed.

The present report deals with a detailed study of the effects of synthetic 11-dehydrocorticosterone in the form of the acetate and the free compound on a patient with Addison's disease who consented to act as a subject. For purposes of comparison, the effects of 17-hydroxy-11-dehydrocorticosterone* (compound E of Kendall) were also studied.

THE PATIENT

The patient in our study was a woman, aged thirty-eight years, who had Addison's disease of seven years' duration, presumably due to bilateral adrenal cortical tuberculosis. During most of the period since the onset of the disease she had been treated with injections of 11-desoxycorticosterone acetate in a dose of 3 mg. daily. She had a solitary, normally functioning left kidney, the right kidney having been removed in 1935 because of renal tuberculosis. In addition, she had chronic rheumatic mitral endocarditis with stenosis and insufficiency. Except for an episode of congestive heart failure in 1940 induced by overtreatment with 11-desoxycorticosterone acetate, her cardiac function had always been adequate and she had remained in reasonably good health.

METHODS OF STUDY

General. Throughout the study the patient lived in a special metabolic unit of the hospital, designed for the careful measurement of intake and output. She was confined to bed only during glucose and insulin tolerance tests. At other times she was up and about the ward. Her activity was approximately uniform from day to day. She was weighed daily before breakfast. Blood pressure determinations were made four times daily. She remained in good general condition throughout the study and consumed her entire diet daily.

Treatment. In order to prevent interruption of the study by adrenal insufficiency,

* The authors are indebted to Dr. E. C. Kendall for the supplies of 17-hydroxy-11-dehydrocorticosterone used in this study.

a basal treatment of 3 mg. of 11-desoxy corticosterone acetate in sesame oil daily, administered intramuscularly, was employed. To the basal treatment were added, during separate periods of study, 50 mg. of 11-dehydrocorticosterone acetate, 200 mg. of 11-dehydrocorticosterone acetate and 20 mg. of 17-hydroxy-11-dehydrocorticosterone daily administered intramuscularly. In addition, during one period, the basal treatment with 11-desoxycorticosterone acetate was discontinued and the patient received only 100 mg. of free 11-dehydrocorticosterone daily. With the exception of 11-desoxycorticosterone acetate, which was given as a single dose each morning, the daily dose of each steroid employed was injected intramuscularly in two equal parts spaced twelve hours apart.*

* *Procedure for making suspensions of steroids.* The weighed samples of steroids were heated in a covered beaker for one hour at 105°C. Dehydrocorticosterone and its acetate were ground to a fine powder in a sterile agate mortar. A portion of the required amount of autoclaved sesame oil was added and grinding was continued until most of the steroid was in suspension. The suspension was transferred with a sterile pipet to a sterile rubber-capped bottle. The mortar was rinsed with successive portions of sesame oil until all of the steroid and all of the required amount of sesame oil had been transferred to the bottle. The pipet was rinsed with 0.5 cc. of acetone which was added to the suspension. A cotton plug was placed in the mouth of the bottle and it was heated one hour in an oven at 105°C. The rubber cap was then put in place and the bottle was shaken until cold to avoid formation of large crystals by the steroid which crystallized out of the oil on cooling. Sesame oil containing 2 per cent of benzyl alcohol was also used but the benzyl alcohol did not increase the solubility of the steroids sufficiently to be of any advantage.

The weighed sample of 17-hydroxy-11-dehydrocorticosterone was dissolved in alcohol, the required amount of sesame oil was added and the alcohol was removed in a vacuum. As soon as the oil became cloudy from separation of the steroid it was transferred to a bottle and heated at 105°C. for two hours. The bottle was capped and shaken until cold.

The concentrations of the various steroids in sesame oil were as follows: 11-dehydrocorticosterone acetate (dose, 50 mg. daily), 25 mg. per cc.; 11-dehydrocorticosterone acetate (dose, 200 mg. daily), 100 mg. per cc.; 11-dehydrocorticosterone (dose, 100 mg. daily), 50 mg. per cc.; 17-hydroxy-11-dehydrocorticosterone (dose, 20 mg. daily), 10 mg. per cc.

A commercial preparation of 11-desoxycorticosterone acetate in sesame oil, containing 5 mg. per cc., was employed.

The usual period of administration of a given steroid was eight or nine days. Urine collections were made each twenty-four hours for the first six days; on the seventh day a glucose tolerance test was performed and on the eighth day an insulin tolerance test. In some instances, the patient was made to fast on the ninth day.

Diet. The diet was weighed. Three menus were employed, each menu twice in each six-day period. The daily intake of carbohydrate averaged 219 Gm., of protein, 61 Gm. and of fat, 68 Gm. The diet was supplemented with 7 Gm. of sodium chloride and 1 Gm. of potassium (in the form of potassium citrate) daily. Figures for the composition of the diet, obtained by direct analysis and addition of the supplements of sodium chloride and potassium in the case of electrolytes and nitrogen, and from standard tables in the case of carbohydrate, protein and fat, are given in Table 1. Water intake (as drinking water) was 1,500 cc. daily.

Studies of Electrolyte Metabolism. Urinary excretion of sodium, potassium, chloride and phosphorus was measured daily during periods of six days each. Plasma sodium, potassium, chloride, carbon dioxide content and urea and hematocrit were determined on venous blood on the first day of each period.

Studies of Carbohydrate Metabolism. Determinations of the fasting blood sugar were made every other morning. Glucose tolerance tests were performed on the seventh day of most periods by administering 0.5 Gm. of glucose per Kg. of ideal body weight in a 20 per cent solution intravenously during a period of thirty minutes. Insulin tolerance tests were performed on the eighth day of most periods by administering 0.05 unit of insulin per Kg. of ideal body weight intravenously, a solution of insulin containing 5 units per cc. being employed. The blood sugar was determined at intervals

during several periods of fasting of twenty-four hours each. All determinations of blood sugar were made on capillary blood. Total urinary nitrogen was estimated daily.

Miscellaneous Studies. Periodic determinations of urinary 17-ketosteroids and "cortin-like" substances were made. Blood cholesterol, cholesterol esters, lecithin, fatty acids and total lipoids, and total serum protein and albumin-globulin ratio were determined at intervals.

Chemical Methods. Blood sugar was determined by the procedure described recently by Somogyi; albumin and total protein in serum by a modification of the biuret procedure of Kingsley; chlorides in plasma by a modification of the method of Keys, and in urine by a modified Volhard-Harvey titration; sodium in plasma and urine by the method of Butler and Tuthill; potassium in plasma and urine by Hartzler's modification of the chloroplatinate method of Shohl and Bennett; inorganic phosphorus in plasma and urine by the method of Gomori; carbon dioxide content[14] and urea[15] of plasma according to the manometric procedures described by Peters and Van Slyke; urinary total nitrogen by the Kjeldahl method; total lipoid fatty acids plus cholesterol in plasma by the method of Bloor; cholesterol and cholesterol esters by the methods of Bloor, and Bloor and Knudson, respectively, and lecithin by the method of Youngburg and Youngburg.

Urinary 17-ketosteroids were determined by the technic of Callow and associates,[5,6] employing a correction equation to compensate for the overestimation due to non-ketonic chromogens. "Cortin-like" substances in urine were estimated by the colorimetric method of Talbot, Saltzman, Wixom and Wolfe.

TABLE I

DAILY INTAKE DATA

Menu	Total, Gm.				Calories	Total, mEq.		
	Carbohydrate	Protein	Fat	Nitrogen		Sodium	Potassium	Chloride
1	220	63	65	10.21	1,717	154	92	173
2	222	60	63	9.52	1,695	168	104	182
3	216	60	75	10.45	1,779	148	98	172
Average	219	61	68	10.06	1,732	157	98	176

RESULTS

Studies of Electrolyte Metabolism. There was little change in the electrolyte pattern of the plasma during the several programs of treatment. (Table II.)

The principal effect of 11-dehydrocorticosterone on electrolyte and water balance was a decrease in the excretion of sodium chloride and water for several days (during period 5) *following* the administration of 200 mg. of the acetate daily for eight days. (Fig. 1, Table III.) At the same time there was a decrease in the excretion of potassium in the urine. During the few days that sodium chloride and water were being retained there was a gain of 2 Kg. of body weight associated with the development of edema and there was a slight rise in mean blood pressure and an increase in cardiac size. These effects occurred after administration of the compound had been stopped

TABLE II

HEMATOCRIT, BLOOD SUGAR, PLASMA UREA AND PLASMA ELECTROLYTE VALUES DURING VARIOUS PROGRAMS OF TREATMENT

Period	Daily Treatment*	Days†	Mg. per 100 cc.		Hematocrit, Per Cent Cells	mEq. per Liter			
			Sugar‡	Urea		CO_2	Chloride	Sodium	Potassium
1	3 mg. DOCA	8	73 (70–83)	30	33	26	106	137	4.9
2	50 mg. DHCA + 3 mg. DOCA	8	81 (71–86)	29	33	25	106	137	4.6
3	3 mg. DOCA	8	76 (73–83)	24	32	27	106	137	4.4
4	200 mg. DHCA + 3 mg. DOCA	8	80 (76–83)	24	31	..	104	135	3.7
5	3 mg. DOCA	14	81 (79–86)	25	30	..	107	139	4.0
6	3 mg. DOCA	6	81 (76–86)	25	34	26	104	134	4.2
7	3 mg. DOCA	6	76 (53–86)	23	35	..	104	133	3.6
8	20 mg. 17-OH-11-DHC + 3 mg. DOCA	9	77 (64–100)	23	33	..	105	134	4.1
9	3 mg. DOCA	12	79 (70–86)	25	34	..	106	136	4.0
10	100 mg. DHC	11	86 (83–89)	24	32	..	107		

* DOCA = 11-desoxycorticosterone acetate; DHCA = 11-dehydrocorticosterone acetate; 17-OH-11-DHC = 17-hydroxy-11-dehydrocorticosterone; DHC = 11-dehydrocorticosterone.

† Refers to the number of days the various steroids were administered before analyses of the blood for electrolytes were performed.

‡ Upper figure is average; figures in parentheses are minima and maxima.

TABLE III

URINARY EXCRETION OF ELECTROLYTES AND NITROGEN DURING VARIOUS PROGRAMS OF TREATMENT*

Period	Treatment	Days†	Average Excretion, mEq. per 24 Hours			Total Nitrogen, Gm. per 24 Hours
			Chloride	Sodium	Potassium	
1	3 mg. DOCA	5‡	149	149	83	7.15
2	50 mg. DHCA + 3 mg. DOCA	6	139	132	85	7.26
3	3 mg. DOCA	6	143	135	90	8.18
4	200 mg. DHCA + 3 mg. DOCA	6	153	147	88	8.02
5	3 mg. DOCA	6	122	130	71	7.99
6	3 mg. DOCA	6	173	177	85	8.60
7	3 mg. DOCA	6	167	167	89	8.45
8	20 mg. 17-OH-11-DHC + 3 mg. DOCA	6	141	148	86	8.70
9	3 mg. DOCA	6	147	146	92	8.36
10	100 mg. DHC	6	142	133	81	8.06

* The same data are charted in Figure 1.

† Refers to number of days of urine collection, not to number of days of administration of the various steroids.

‡ Specimen for one day of the six-day collection period was lost.

and could reasonably be attributed to a delayed action of the compound owing to its low solubility in the tissue fluids.* Coinciding with these changes there was an increase in "cortin-like" compounds in the urine. (Table IV.) These effects gradually reversed themselves during the succeeding two periods.

but was followed by retention of sodium and chloride despite continued administration of the compound, so that the average daily excretion for the period was approximately the same as during control periods.

TABLE IV

URINARY EXCRETION OF 17-KETOSTEROIDS AND "CORTIN-LIKE" COMPOUNDS DURING VARIOUS PROGRAMS OF TREATMENT

Daily Treatment	17-Ketosteroids		"Cortin-like" Compounds	
	Determinations	Average Excretion, Mg. per 24 Hours	Determinations	Average Excretion, Mg. per 24 Hours*
3 mg. DOCA	3	0.7	4	0.051
50 mg. DHCA + 3 mg. DOCA	1	0.3	7	0.091
3 mg. DOCA	2	1.1	5	0.060
200 mg. DHCA + 3 mg. DOCA	2	0.8	8	0.172
3 mg. DOCA	..	...	2	0.303†
3 mg. DOCA	3	1.1	5	0.077
20 mg. 17-OH-11-DHC + 3 mg. DOCA	2	0.8	3	0.234
3 mg. DOCA	..	..	4	0.084
100 mg. DHC	..	..	11	0.245

* The quantity of "cortin-like" compounds is expressed in terms of mg. of 11-dehydrocorticosterone.

† Determinations made on the two days immediately following cessation of treatment with 200 mg. of 11-dehydrocorticosterone acetate daily.

During and after the period of administration of 50 mg. of 11-dehydrocorticosterone acetate daily (period 2), there was a slight decrease in excretion of sodium chloride, of questionable significance. During the period of administration of 100 mg. of free 11-dehydrocorticosterone daily (period 10) there was a progressive decrease in excretion of sodium chloride associated with a gain of body weight. (Fig. 1.)

During the first two days of administration of 20 mg. of 17-hydroxy-11-dehydrocorticosterone daily, the excretion of sodium and chloride in the urine increased. However, this increase not only failed to persist

* It is to be noted that these changes were first observed three days before a menstrual period, that is, at a time when menstrual edema might be expected to occur. However, this explanation for the retention of salt and development of edema seemed to be ruled out by the fact that the patient never before or subsequently had frank edema preceding menstruation.

Studies of Carbohydrate Metabolism. Changes in the level of the fasting blood sugar during the various programs of treatment were of small magnitude and probably not significant. (Table II.) Variations in urinary nitrogen were of small magnitude. (Fig. 1.)

Likewise, there was little or no alteration in the blood sugar curves during glucose tolerance tests. (Fig. 2.)

Insulin tolerance tests showed a smaller maximal depression of the blood sugar level and a higher blood sugar level at the conclusion of the test when the patient was receiving 200 mg. of 11-dehydrocorticosterone acetate or 20 mg. of 17-hydroxy-11-dehydrocorticosterone daily than when she was receiving the basal treatment alone. (Fig. 3.) In view of the limited amount of data, the changes are probably not of sufficient magnitude to be clearly attributed to the compounds in question but they are suggestive of an effect on carbohydrate

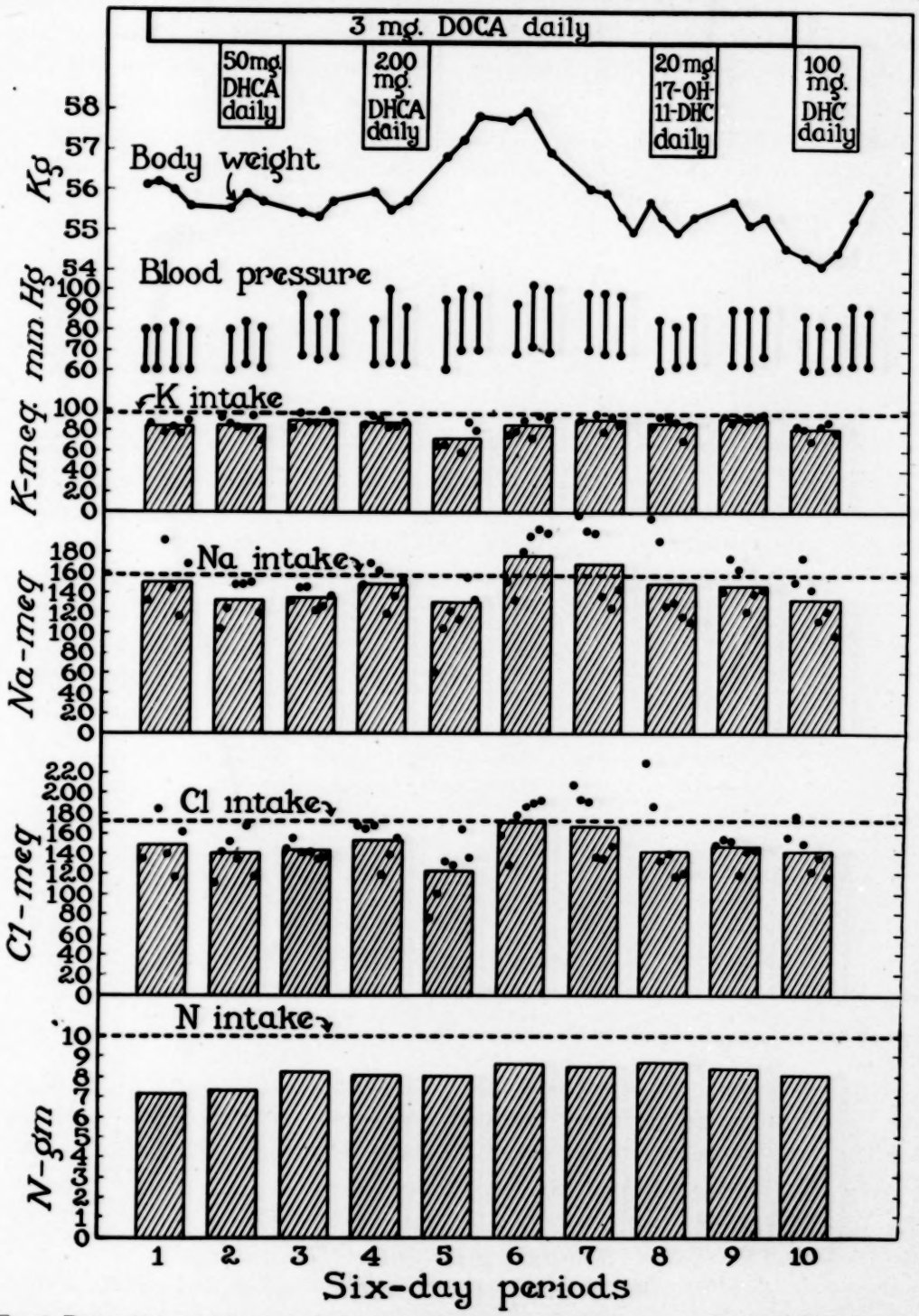

FIG. 1. Data relative to treatment, body weight, blood pressure and urinary excretion of potassium, sodium, chloride and nitrogen in a patient with Addison's disease. DOCA is 11-desoxycorticosterone acetate; DHCA, 11-dehydrocorticosterone acetate; 17-OH-11-DHC, 17-hydroxy-11-dehydrocorticosterone; DHC, 11-dehydrocorticosterone. Cross-hatched columns represent average daily excretion; dots represent daily excretion.

metabolism. The changes were most marked in the case of 17-hydroxy-11-dehydrocorticosterone.

Hypoglycemia occurring in the course of insulin tolerance tests seemed to be better tolerated (subjectively) when the patient was receiving either 11-dehydrocorticosterone, 11-dehydrocorticosterone acetate or 17-hydroxy-11-dehydrocorticosterone than when the basal treatment with 11-desoxycorticosterone acetate alone was employed. The subjective improvement, while not susceptible of measurement, seemed to be most marked when she was receiving 17-hydroxy-11-dehydrocorticosterone.

During the course of a fast of twenty-four hours there was less fall of the blood sugar while the patient was receiving either 100 mg. of 11-dehydrocorticosterone, 200 mg. of 11-dehydrocorticosterone acetate or 20 mg. of 17-hydroxy-11-dehydrocorticosterone daily than when she was receiving 11-desoxycorticosterone acetate alone. (Fig. 4.) While the differences in decline of the blood sugar during the several fasts were not great, they were of sufficient magnitude to be suggestive of some carbohydrate activity on the part of free 11-dehydrocorticosterone and 17-hydroxy-11-dehydrocorticosterone, particularly the latter compound.

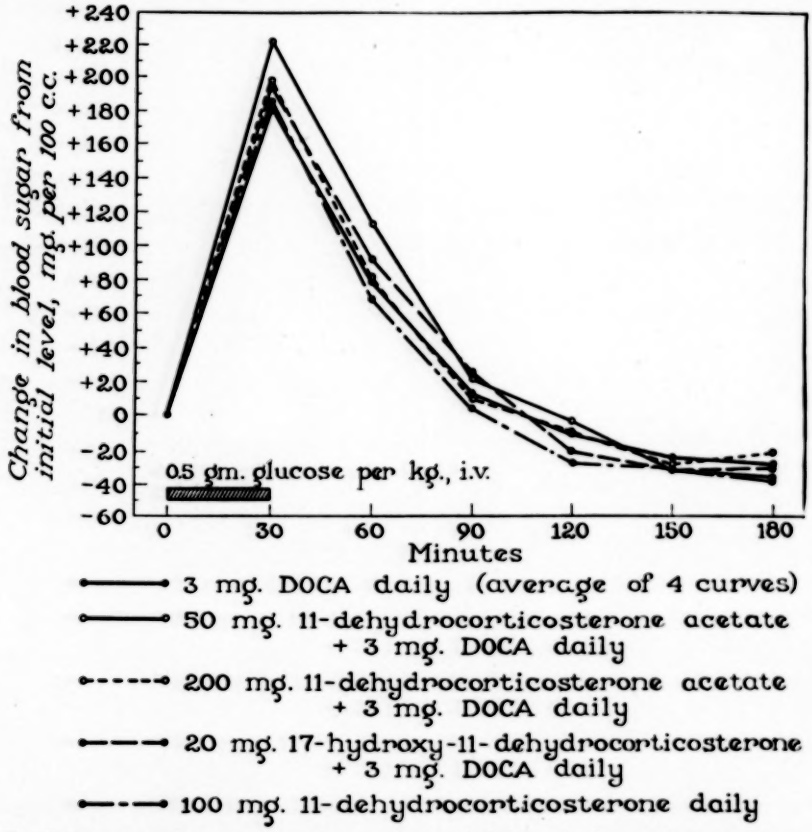

FIG. 2. Glucose tolerance curves in a patient with Addison's disease during various programs of treatment. The points of each curve are charted as change in blood sugar from starting level, in milligrams per 100 cc.

Other Studies. The administration of 11-dehydrocorticosterone and of 17-hydroxy-11-dehydrocorticosterone resulted in moderate increases of "cortin-like" compounds in the urine. (Table IV.) No significant change in the urinary excretion of 17-ketosteroids was noted.

No consistent effects of the various programs of treatment on blood lipoids, serum proteins, albumin-globulin ratio or urinary phosphorus were observed.

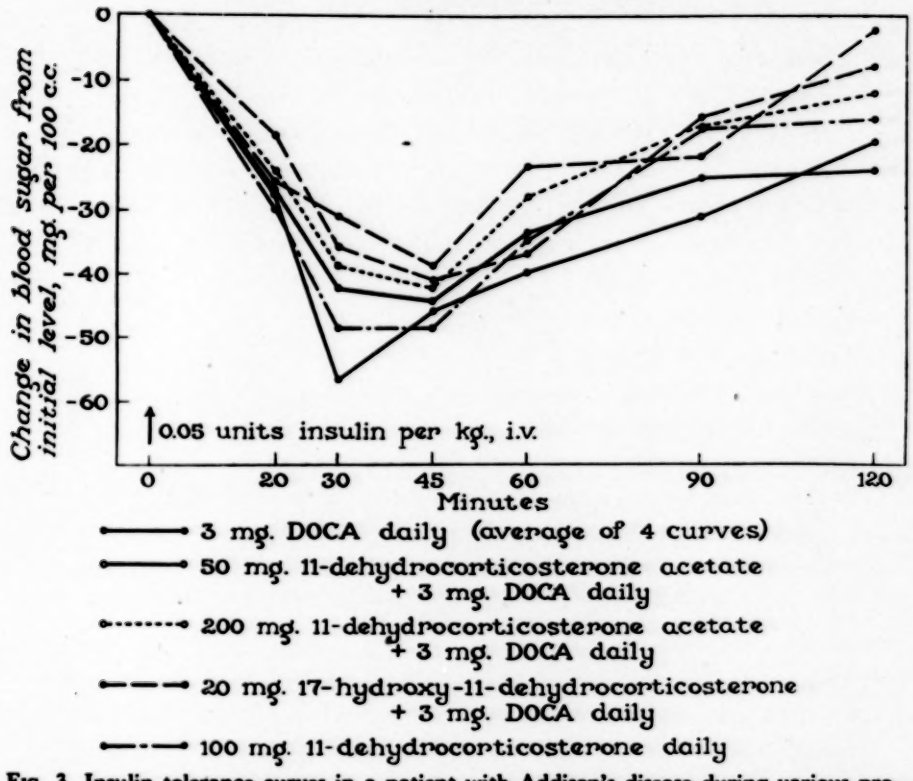

FIG. 3. Insulin tolerance curves in a patient with Addison's disease during various programs of treatment. The points of each curve are charted as change in blood sugar from starting level, in milligrams per 100 cc.

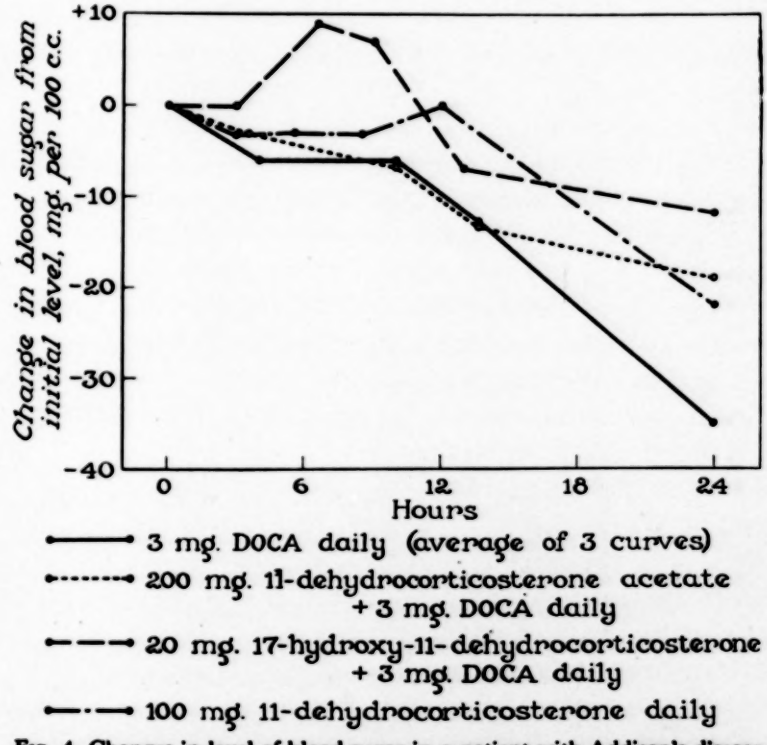

FIG. 4. Changes in level of blood sugar in a patient with Addison's disease during twenty-four hour fast on various programs of treatment. In each instance the period of fasting was considered as beginning in the morning at 0 hour which was fourteen hours after the last meal.

COMMENT

Studies on animals have clearly demonstrated that 11-dehydrocorticosterone is capable of influencing the metabolism of carbohydrate and electrolytes. The present study, and also other recent studies, indicate that it is not a simple matter to demonstrate these activities in the human subject.

The observations which we have recorded indicate that the compound in doses up to 200 mg. of the acetate daily has a slight influence on electrolyte metabolism as indicated by retention of sodium chloride and water. The data disclose no more than a hint of carbohydrate activity in the form of minor alterations of the insulin tolerance curve and the blood sugar during fasting. It seems probable that the carbohydrate and electrolyte effects which have been clearly demonstrated in animals could be duplicated in the human subject if it were possible to expose the tissues to a higher concentration of the steroid. Unfortunately, the low solubility of the compound limits the amount which can be conveniently introduced into any given subject by parenteral injection.

As already noted, this patient had only one kidney. Forsham, Thorn, Bergner and Emerson suggested that the total mass of functioning renal tissue might be a limiting factor in the response to the compound, as measured by its effects on nitrogen and electrolyte excretion. This seems to be a reasonable suggestion and may account, in part at least, for the minimal "renal response" of our patient to the compound. However, even taking into account the possible functional limitations of a solitary kidney, it is difficult to escape the conclusion that 11-dehydrocorticosterone in the doses employed was, by comparison with 11-desoxycorticosterone acetate, relatively deficient in electrolyte activity.

In this patient 17-hydroxy-11-dehydrocorticosterone in a dose of 20 mg. daily did not produce as striking changes in carbohydrate metabolism as have been observed in patients with coexisting Addison's disease and diabetes in response to even smaller doses. Nevertheless, the observations made on this latter group of patients as well as data from numerous experiments on animals, leave no room for doubt that the carbohydrate activity of 17-hydroxy-11-dehydrocorticosterone is much greater than that of 11-dehydrocorticosterone.

In the present study it was noted that 17-hydroxy-11-dehydrocorticosterone induced only a transient increase in sodium excretion, which did not persist with continued administration of the compound. This observation suggests that the increase in sodium and chloride excretion which has been observed after only a single injection of this compound[19] may not provide an adequate basis for a description of its electrolyte activity.

It appears, on the basis of this study, as well as others, that 11-dehydrocorticosterone will have a very limited clinical usefulness, if any, in the treatment of Addison's disease, unless it should prove feasible to administer relatively tremendous doses, perhaps by mouth, at reasonable cost to the patient. Nevertheless, the physiologic effects and metabolism of this steroid, as well as other pure steroids of adrenal origin, deserve further study in human subjects. It is therefore to be hoped that the shortcomings of 11-dehydrocorticosterone as a therapeutic tool will not result in its becoming unavailable for further experimental study.

SUMMARY AND CONCLUSIONS

1. A study of the effects of synthetic 11-dehydrocorticosterone (both the acetate and the free compound) on a patient with Addison's disease was carried out. Doses from 50 to 200 mg. daily were employed. The effects of 17-hydroxy-11-dehydrocorticosterone in a dose of 20 mg. daily were also studied.

2. After a period of administration of

11-dehydrocorticosterone acetate in a dose of 200 mg. daily there was a decrease in the urinary excretion of sodium chloride and water, a gain of body weight due to edema, a slight rise in blood pressure and an increase in cardiac size. There was also a decrease in urinary excretion of salt and water during a period of administration of 100 mg. of free 11-dehydrocorticosterone daily.

3. Effects of 11-dehydrocorticosterone on carbohydrate metabolism, studied by means of determinations of the fasting blood sugar, glucose and insulin tolerance tests, changes in the blood sugar during prolonged fasting and estimations of urinary nitrogen, were slight and in most instances of questionable significance.

4. The administration of 17-hydroxy-11-dehydrocorticosterone in a dose of 20 mg. daily resulted in a transient increase in the urinary excretion of sodium chloride. The compound in this dose had slight carbohydrate effects, as indicated by a diminished hypoglycemic response to insulin and better maintenance of the blood sugar level during fasting.

5. Both 11-dehydrocorticosterone and 17-hydroxy-11-dehydrocorticosterone produced increases in the urinary excretion of "cortin-like" substances in the urine. Neither produced any change in the urinary excretion of 17-ketosteroids.

6. Neither compound produced consistent changes in blood lipoids, serum proteins, albumin-globulin ratio or urinary phosphorus.

The authors are indebted to Miss Lida Burrill, chief dietitian, Mayo Clinic metabolic unit, St. Marys Hospital, for her careful planning and supervision of the diets used in this study.

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Sodium Loss in Man Induced by Desoxycorticosterone Acetate*

Study in a Subject with Myotonic Dystrophy

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DESOXYCORTICOSTERONE acetate (DCA) administered in large doses to normal dogs causes polydipsia and polyuria which then disappear within about one week of withdrawal of the steroid.[7,12] These results do not appear in normal cats to whom DCA is exhibited.[19] Normal man, given smaller doses for a time shorter than necessary to produce polydipsia and polyuria in dogs, responds to DCA by retaining sodium and water.[15]

The purpose of this paper is to report the production by DCA of a syndrome, reminiscent of that which occurs in dogs, in a patient with myotonic dystrophy. In an effort to understand the mechanism of this syndrome, we have measured the effects of DCA on the overall nitrogen, sodium and potassium metabolism and on certain renal glomerular and tubular processes.

PLAN OF STUDY AND METHODS

The subject, B. R., Unit No. 393446, was a fifty-eight year old white male with myotonic dystrophy. In addition to profound muscle atrophy and myotonia, the patient had a non-toxic nodular goiter, bilateral testicular atrophy and gynecomastia. Daily excretion of the follicle-stimulating hormone was not elevated.† With the exception of a depressed excretion of 17-ketosteroids† (2 mg. per day), there were no stigmata of corticoadrenal disease prior to DCA administration. Serum concentrations of sodium (144 mEq./L.) and of potassium (4 mEq./L) were normal and the patient responded to sodium restriction (27 mEq. of sodium daily for ten days) by retaining sodium in a fashion compatible with normal corticoadrenal function.

DCA in oil** was administered intramuscularly in doses of 5 to 15 mg. daily for seventeen days and, after an interval of seventy days, 10 mg. daily for ten days.

The patient was maintained on a constant diet calculated to contain 50.4 Gm. of protein, 149.4 Gm. of carbohydrate, 60.7 Gm. of fat and 1,345 calories. Sodium intake was regulated by supplementing a sodium-poor diet with enteric-coated[1] sodium chloride tablets. The diet was analyzed periodically for nitrogen by a macro-Kjeldahl method[1] and for sodium and potassium by the flame photometer.[5] Stools for each period were pooled and analyzed for nitrogen, sodium and potassium. Urine was collected daily and preserved with 10 ml. of 25 per cent acetic acid. The excretion of nitrogen, sodium, potassium and, during the latter half of the study, chloride (by the method of Harvey[6]) was measured. Serum sodium and potassium concentrations and the concentrations of glucose and of non-protein

† These measurements were kindly done by Drs. Lawson Wilkins and Roger A. Lewis, Department of Pediatrics.

** Percorten, generously supplied by Ciba Pharmaceutical Products, Inc.

* From the Physiological Division, Department of Medicine, The Johns Hopkins University and Hospital, Baltimore, Md. The work was done under a contract between the Office of Naval Research, U. S. Navy Department and the Johns Hopkins University.

nitrogen in the blood were determined at intervals.

Water intake was unrestricted. The difference between water intake and urine volume was assumed to be a function of fluid balance. Body weight was recorded daily. Creatine was measured by the method of Peters.[11]

RESULTS

The overall balances of nitrogen, electrolytes and water appear in Table 1 and Figure 1.

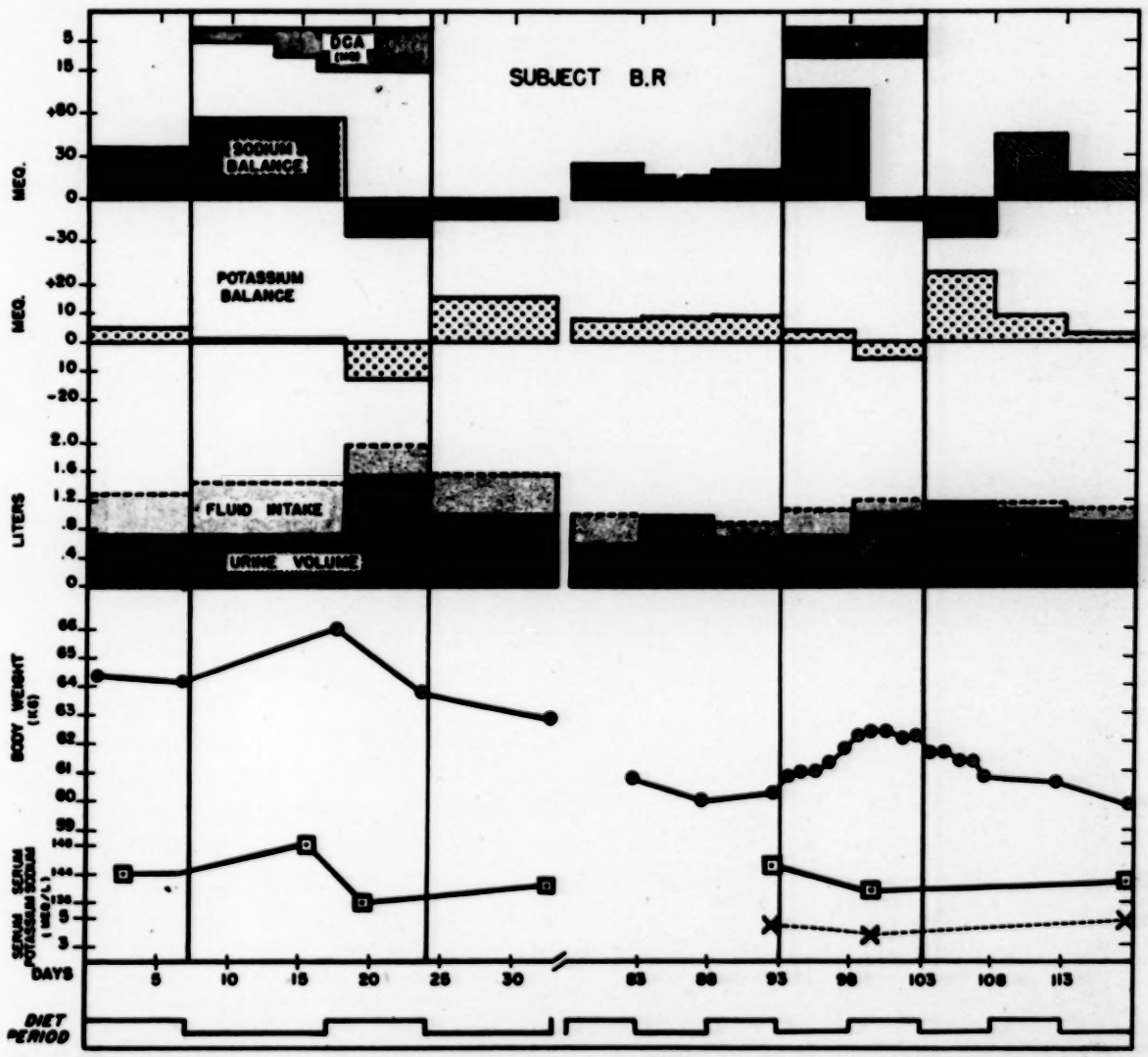

FIG. 1. Effect of DCA on sodium and on potassium balance, on fluid intake, urine volume, body weight and concentrations of sodium and of potassium in serum. Balances, fluid intakes and urine volume are charted as averages for each diet period. (See Table 1 for daily data.)

The simultaneous renal clearances of mannitol, by the single injection technic of Newman et al.,[10] and of creatine were measured prior to the first course of DCA and repeated on the last day of the first course. Creatine clearance was measured during rising serum concentrations following the ingestion of 25 Gm. of creatine hydrate.

Observations during the second period of study were similar to those of the first. The initial effects of DCA were retention of sodium and of chloride, less positive potassium balance, unaltered nitrogen balance, water retention with a corresponding increase in body weight and the appearance of mild edema of the face.

TABLE I

METABOLIC DATA FROM EXPERIMENTS I AND II IN SUBJECT B. R.

Day	Fluid Intake (Ml.)	Urine Volume (Ml.)	Sodium (mEq.)			Potassium (mEq.)			Chloride (mEq.) Urine	Nitrogen (Gm.)			DCA* (Mg.)
			Diet	Urine	Fecal	Diet	Urine	Fecal		Diet	Urine	Fecal	
1	....	950	158	116	8	56	40	14	...	8.9	5.2	1.1	
2	590	1100	158	163	8	56	52	14	...	8.9	8.3	1.1	
3	1370	650	158	88	8	56	..	14	...	8.9	6.8	1.1	
4	1420	600	158	83	8	56	39	14	...	8.9	6.6	1.1	
5	1830	750	158	97	8	56	34	14	...	17.9	8.7	1.1	
6	....	....	158	...	8	56	..	14	...	8.9	....	1.1	
7	1570	800	158	136	8	56	35	14	...	8.9	8.1	1.1	
8	1270	600	160	63	7	55	48	12	...	8.3	6.6	1.1	5
9	1370	600	160	70	7	55	48	12	...	8.3	6.8	1.1	5
10	1700	600	160	74	7	55	35	12	...	8.3	5.3	1.1	5
11	1795	750	160	101	7	55	..	12	...	8.3	6.8	1.1	5
12	1820	650	160	84	7	55	41	12	...	8.3	5.8	1.1	5
13	1445	1300	160	176	7	55	46	12	...	8.3	6.9	1.1	5
14	1120	700	160	85	7	55	40	12	...	8.3	6.1	1.1	10
15	1370	1100	160	153	7	55	49	12	...	8.3	6.8	1.1	10
16	1470	840	160	100	7	55	..	12	...	17.3	9.0	1.1	10
17	....	....	160	77	7	55	23	12	...	8.3	3.6	1.1	15
18	2120	600	193	81	7	43	31	14	...	8.4	5.3	0.9	15
19	1520	1150	193	175	7	43	41	14	...	8.4	6.5	0.9	15
20	2070	1850	193	221	7	43	43	14	...	8.4	5.6	0.9	15
21	1920	1520	193	210	7	43	43	14	...	8.4	6.5	0.9	15
22	1995	1870	193	167	7	43	45	14	...	8.4	6.0	0.9	15
23	1770	1370	193	188	7	43	39	14	...	14.7	8.4	0.9	15
24	....	....	193	...	7	43	..	14	...	8.4	...	0.9	15
25	1330	650	161	81	7	48	10	9	...	8.0	5.0	1.0	
26	1770	1100	161	152	7	48	11	9	...	8.0	5.2	1.0	
27	2070	1170	161	185	7	48	..	9	...	8.0	5.9	1.0	
28	1370	1170	161	206	7	48	17	9	...	8.0	6.0	1.0	
29	1270	1400	161	189	7	48	22	9	...	8.0	6.2	1.0	
30	1370	1200	161	175	7	48	..	9	...	8.0	6.8	1.0	
31	1370	940	161	137	7	48	19	9	...	8.0	4.7	1.0	
32	1460	720	161	205	7	48	34	9	...	8.0	6.8	1.0	
33	1470	1300	161	182	7	48	43	9	...	8.0	7.3	1.0	
79	980	780	159	162	15	50	41	10	144	8.3	8.5	1.1	
80	830	540	159	106	15	50	33	10	113	8.3	6.2	1.1	
81	780	600	159	127	15	50	32	10	121	8.3	6.4	1.1	
82	1330	540	159	101	15	50	35	10	105	8.3	6.6	1.1	
83	1180	525	159	111	15	50	28	10	105	8.3	5.5	1.1	
84	1270	1070	164	171	8	65	41	10	159	9.5	6.6	0.9	
85	930	1070	164	150	8	65	43	10	152	9.5	8.6	0.9	
86	780	630	164	59	8	65	22	10	53	9.5	2.1	0.9	
87	1280	1000	164	181	8	65	75	10	187	9.5	8.4	0.9	
88	730	810	164	125	8	65	41	10	113	9.5	6.2	0.9	
89	1180	810	154	124	10	65	41	12	113	9.2	6.2	1.3	
90	970	750	154	81	10	65	37	12	76	9.2	4.3	1.3	
91	730	1100	154	132	10	65	44	12	170	9.2	5.7	1.3	
92	930	615	154	94	10	65	34	12	104	9.2	4.8	1.3	
93	580	1310	154	199	10	65	54	12	174	9.2	7.3	1.3	
94	1290	620	154	65	10	66	58	12	80	8.9	5.2	1.3	10
95	1070	700	154	60	10	66	55	12	74	8.9	10.8	1.3	10
96	970	700	154	61	10	66	54	12	74	8.9	6.3	1.3	10
97	1170	900	154	92	10	66	66	12	107	8.9	7.9	1.3	10
98	905	510	154	62	10	66	28	12	74	8.9	2.6	1.3	10
99	1620	650	158	59	10	56	45	12	87	9.1	4.8	1.3	10
100	730	1325	158	182	10	56	70	12	200	9.1	6.7	1.3	10

TABLE I—(*Continued*)

Day	Fluid Intake (Ml.)	Urine Volume (Ml.)	Sodium (mEq.)			Potassium (mEq.)			Chloride (mEq.) Urine	Nitrogen (Gm.)			DCA* (Mg.)
			Diet	Urine	Fecal	Diet	Urine	Fecal		Diet	Urine	Fecal	
101	1770	....	158	...	10	56	..	12	....	9.1	...	1.3	10
102	930	1250	158	174	10	56	33	12	163	9.1	5.5	1.3	10
103	970	1125	158	128	10	56	51	12	132	9.1	5.6	1.3	10
104	930	1150	167	165	6	69	34	8	150	9.5	5.7	1.1	
105	1130	1150	167	167	6	69	33	8	135	9.5	6.3	1.1	
106	930	1100	167	186	6	69	33	8	178	9.5	6.6	1.1	
107	1170	1275	167	208	6	69	43	8	...	9.5	6.3	1.1	
108	1210	1310	167	210	6	69	41	8	206	9.5	6.1	1.1	
109	1220	1400	170	183	6	80	47	15	184	10.5	5.2	1.4	
110	1400	1160	170	128	6	80	56	15	124	10.5	6.8	1.4	
111	1270	1250	170	118	6	80	70	15	139	10.5	3.2	1.4	
112	1220	1000	170	111	6	80	77	15	112	10.5	4.8	1.4	
113	880	....	170	...	6	80	..	15	...	10.5	...	1.4	
114	1180	1000	145	124	5	65	52	11	120	9.7	6.8	1.3	
115	1170	1000	145	138	5	65	63	11	136	9.7	7.8	1.3	
116	930	600	145	104	5	65	42	11	103	9.7	4.8	1.3	
117	1260	950	145	143	5	65	38	11	122	9.7	5.0	1.3	
118	830	860	145	101	5	65	60	11	100	9.7	5.7	1.3	

* Desoxycorticosterone acetate.

TABLE II

EFFECT OF DCA ON EXCRETION OF CREATINE (SUBJECT B. R.‡)

Time (Min.)	Urine Flow (Ml./min.)	Mannitol Clearance (Ml./min.)	Mannitol U/P*	Creatine			Creatine Mannitol Clearance Ratio
				Serum (Mg. %)	Urine (Mg. %)	Clearance (Ml./min.)	
I. Before Administration of DCA†							
0	Mannitol, 20 Gm. in 80 ml., single injection I. V.						
9	Creatine, 25 Gm. by mouth in 440 ml. water						
27	2.4	46.7	19.4	3.2	24	17.8	0.38
47	2.6	54.0	20.9	9.5	135	37.0	0.68
69	3.4	52.7	15.7	24.0	261	37.0	0.70
90	4.3	42.9	10.0	28.7	221	33.1	0.79
II. On 17th Day of DCA Administration (First Course)							
0	Mannitol, 20 Gm. in 80 ml., single injection I. V.						
17	Creatine, 25 Gm. by mouth in 440 ml. water						
41	5.7	65.9	11.6	9.1	110	68.7	1.04
63	11.5	80.5	7.0	18.5	143	88.0	1.09
88	3.5	48.2	13.8	24.3	306	44.5	0.93

* Urine mannitol concentration/serum mannitol concentration.
† Desoxycorticosterone acetate.
‡ Surface area: 1.68 sq. m.

After six to ten days of continuous treatment with DCA, changes in the movement of electrolytes and water occurred. Sodium excretion increased above control levels, ultimately producing a strongly negative sodium balance which was not reversed by

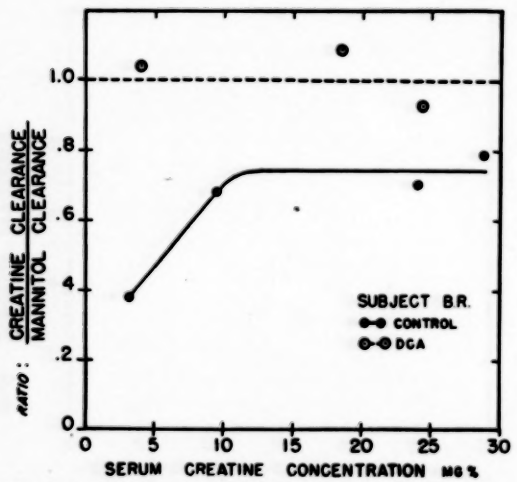

FIG. 2. Renal tubular reabsorption of creatine before and during administration of DCA. Reabsorption is a function of the ratio of creatine clearance to glomerular filtration (mannitol clearance). Note that during DCA treatment the ratio approximated 1.0 indicating that creatine was not reabsorbed.

augmenting dietary sodium. Chloride moved with sodium; the potassium balance became negative. There was a mild diuresis and, despite an increase in voluntary water intake, the difference between intake and urine output was decreased. Body weight decrease was commensurate with loss of water. No changes in muscle strength or in degree of myotonia were observed.

During the first five to ten days following withdrawal of DCA negative sodium balance persisted. There was an immediate marked potassium retention which diminished to normal balance over a ten-day period. Diuresis and augmented water intake continued as long as sodium was being lost. Decrements in body weight paralleled those of water balance. Following the first course of DCA there was a brief increase in nitrogen balance. This phenomenon did not occur during recovery from the second course of DCA.

The concentration of sodium in the serum rose to 148 mEq./L. during the early days of DCA administration and fell during the period of diuresis to 136 mEq./L. Serum potassium concentration decreased but remained within the accepted normal range. It is of interest to note that the patient complained spontaneously that his food tasted excessively salty at the time the serum sodium concentration was highest and that this complaint ceased during the period of diuresis.

As in experiments with the dog,[19] the glomerular filtration rate was uninfluenced by prolonged DCA administration. Urine flow was augmented and the ratio of urine mannitol concentration to serum mannitol concentration was decreased, indicating diminished water reabsorption by the renal tubule. Reabsorption of creatine by the renal tubules was blocked completely by DCA even at low serum creatine concentration. (Table II, Fig. 2.)

During the periods of DCA administration arterial systolic pressure tended to increase (range, 118 to 144 mm. Hg) above the control range (112 to 120 mm. Hg). Arterial diastolic pressure (70 to 84 mm. Hg) did not change. No modification of the concentrations of blood glucose or nonprotein nitrogen occurred.

COMMENTS

The response to DCA elicited in a patient with myotonic dystrophy, a disease characteristically associated with testicular atrophy and possibly with derangement of other endocrine glands, may not represent the response to be expected in normal man. Nevertheless, the evidence in this patient indicated that corticoadrenal function was normal with respect to electrolyte economy prior to DCA administration. The effects of DCA administration in our subject may be divided for purposes of analysis into the early, late and withdrawal phases.

The early effects are the familiar ones described in normal man by Thorn and Emerson[15] and qualitatively resemble the effects of DCA treatment of patients with

Addison's disease and of adrenalectomized animals: sodium, chloride and water retention, potassium loss and weight gain.[4,9,16,17,18]

The late effect on water metabolism in the subject herein described resembles that seen in the normal dog subjected to a similar regimen. The mechanism responsible for DCA-induced diuresis remains a matter of speculation. Ragan et al.[12] suggest that polyuria in the dog under these circumstances is secondary to polydipsia. These workers observed that in the dog, in which the syndrome of polyuria and polydipsia had been established by large doses of DCA, water restriction caused a rise in serum sodium concentration and a fall in urine volume. Although our patient complained of thirst during the early phase of DCA administration and subsequently voluntarily increased his water intake, most of the data at hand point toward a primary renal mechanism. The composition of the urine was unlike that described in water diuresis in which urine is dilute with respect to chloride[8,20] and presumably with respect to sodium. Despite the moderate diuresis occurring during DCA administration the urinary concentrations of sodium, chloride and potassium increased. (Table 1.) Creatinuria cannot be increased by forced water diuresis,[21] a fact which renders it improbable that accelerated urine flow was primarily responsible for the reduction in tubular capacity for reabsorbing creatine. For these reasons it is unlikely that enhanced water intake is the primary mechanism responsible for the syndrome. Increased excretion of sodium, chloride, potassium, water and creatine suggests that widespread inhibition of certain renal tubular reabsorptive functions may have taken place.

When DCA is withdrawn, the pattern of electrolyte balance (sodium, chloride and water loss, marked potassium retention) resembles that of patients with Addison's disease and suggests that some hypofunction of the adrenal cortex has been induced. That corticoadrenal atrophy can be produced by DCA has been demonstrated anatomically.[2,13,14] Fortunately, the evidence of reduced corticoadrenal function in this patient did not persist beyond ten days.

The possibility that atrophy so induced may not be regularly reversible has discouraged us from inquiring in normal man into the cause of the inhibition of renal tubular reabsorption associated with prolonged exhibition of DCA.

It is of interest that dogs in which polyuria was induced by DCA developed weakness associated with loss of muscle potassium.[3] The subject observed here showed no such impairment of motor power. The discrepancy may be due to the fact that the doses of DCA were smaller in man (0.08 to 0.25 mg./Kg.) than in the dog (1.6 mg./Kg.) and that administration of DCA was terminated in order to avoid loss of potassium sufficient to produce serious derangement of the intracellular electrolyte pattern.

The assumption has been made that this subject responded to DCA in a manner which represents the normal. This may be proved subsequently to be untenable. His response to DCA may be related to his underlying myotonic dystrophy although evidence for this is lacking.

SUMMARY

1. Two courses of DCA, in doses varying from 5 to 15 mg. a day, were given to a patient with myotonic dystrophy.

2. During the second week of DCA administration there was an increase in voluntary fluid intake, a diuresis with reduction in water balance, negative sodium and potassium balances and loss of body weight. The glomerular filtration rate was unchanged. Reabsorption of water and of creatine was inhibited.

3. During the week following withdrawal of DCA, after polydipsia, polyuria and electrolyte loss had been established, the pattern of electrolyte balance resembled that of Addison's disease.

The authors are indebted to Miss Rachel Fee, nurse-in-charge of the metabolism ward and Miss Liana Cernoia, dietitian-in-charge of the metabolism ward, for their contributions to this study.

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Effect of Increasing the Blood Volume and Right Atrial Pressure on the Circulation of Normal Subjects by Intravenous Infusions*

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MANY observations on the effects of decreasing the blood volume in man have been reported, but much less information is available on the effects of increasing the blood volume. It is known that an increase in blood volume caused by the rapid intravenous administration of fluid will produce a rise in venous pressure. The effects of this rise in venous pressure on the cardiac output and the size of the heart are of considerable importance to the physician. If, as the venous pressure rises, the normal heart is dilated and the cardiac output greatly increased, this would indicate that a considerable strain was being placed upon the heart. Such a reaction might explain the poor tolerance of patients with heart failure to intravenous fluids.

METHODS

Normal young volunteer subjects were used for the various studies. Blood volume changes were produced by the rapid intravenous administration of fluids through a No. 17 gauge needle in an antecubital vein. The rate of infusion varied from 32 to 77 cc. per minute. Physiological saline solution and 5 per cent human serum albumin† in physiological saline solution were used. All studies except those relating to heart size were carried out under basal conditions. The subjects in all instances remained in the horizontal position for at least thirty minutes prior to any observations.

The right atrial pressure was measured by means of a water manometer attached to a catheter extending through the venous system to the right atrium.[1,2] A point 5 cm. below the fourth right costochondral junction was used as the reference point. Cardiac output determinations were carried out utilizing the direct Fick principle.[1,2] In most instances the arterial pressure was recorded from the femoral artery by the method of Hamilton.[3] Heparin was used as the anticoagulant in the hematocrit tubes. Plasma proteins were determined by the falling drop method.[4] Hemoglobin content of the blood was measured as oxyhemoglobin in an alkaline solution by means of a photoelectric colorimeter. Plasma volume was determined in a few instances by means of the blue dye T 1824. In the remainder, the changes in blood volume were calculated from changes in hematocrit reading assuming a normal initial blood volume based on surface area.

The studies on heart size were carried out at another time; teleoroentgenograms were made of the heart with the subject in the horizontal position. The transverse diameter of the heart, determined from these films,

† The products of plasma fractionation employed in this work were developed from blood collected by the American Red Cross and the Department of Physical Chemistry, Harvard Medical School, Boston, Mass., under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University.

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was used as a measure of heart size. Care was taken to have the position of the diaphragm at nearly the same level for each film.

RESULTS

Ten normal subjects received intravenous infusions of physiological saline solution varying in amount from 750 to 1,825 cc. The infusions were given at a rate of 43 to 77 cc. per minute. Before the infusions were started, control measurements were made. Additional observations were made soon after completion of the intravenous infusion and usually some time later when a major portion of the infused fluid had left the vascular system. These data are recorded in Table I.

Seven other subjects received 1,000 cc. of physiological saline solution containing 50 Gm. of albumin. This produced a relatively isotonic and isoncotic fluid. These data are recorded in Table II.

Two subjects received 1,000 cc. of albumin solution and x-ray studies of the heart size were made. The transverse diameter of the heart was measured on both control and postinfusion films.

There was no evidence that rapid intravenous infusions given at the rate used in the present studies overloaded or adversely affected the circulation. The initial effects of the saline and albumin solutions were essentially the same. They differed in that the saline solution left the vascular system rapidly, whereas the albumin-containing fluid remained in the vascular system for a longer period of time. The infusion produced no symptoms. The neck veins became visible as the venous pressure rose; there was no change in skin color.

In all instances the infusions caused an increase in plasma volume demonstrated either by fall in the hematocrit reading or by actual measurements of the plasma volume by the dye technic. With the saline solution there was also a change in plasma protein concentration. The increase in plasma volume following saline solution was relatively smaller and less prolonged than that following albumin solution.

In all instances there was an elevation of the central venous (right atrial) pressure. This varied from 30 to 95 mm. of water following saline solution and from 60 to 130 mm. of water following albumin solution. Other observers have noted similar changes.[5,6] The rise in atrial pressure appears to represent merely the greater filling of the vascular system with a general elevation of pressure and consequent distention of the least rigid parts. This is similar to the rise in static venous pressure in patients with congestive failure described by Starr.[7]

The cardiac output was measured before and after infusions in all subjects. The infusions produced somewhat variable responses. The changes in cardiac output bear no direct relationship to elevation in the right atrial pressure nor any other observed function of the cardiovascular system. The importance of making observations before, during and after the administration of fluid is emphasized by the study of the data recorded here. If the subject is apprehensive before the fluid is given and becomes more relaxed during the procedure, the cardiac output will fall; if he is relaxed at the beginning of the study and becomes restless as the observations are continued, the cardiac output will rise. These changes are not related to the changes in atrial pressure caused by the increased blood volume. This can be demonstrated by a third determination after the atrial pressure has fallen toward the control level. Results similar to ours following infusion of the albumin solution have been obtained in another laboratory in this country.[8] Other observers have found a moderate change in cardiac output proportional to the change in the right atrial pressure.[9] We are unable to explain the

TABLE I

NORMAL SUBJECTS RECEIVING PHYSIOLOGICAL SALINE SOLUTION

Patient	Remarks	Rate of Injection	Surface Area	Oxygen Consumption	A-V Oxygen Difference	Cardiac Index	Hematocrit Reading	Hemoglobin	Total Protein	Arterial Pressure			Pulse Rate	Atrial Pressure
										Systolic	Diastolic	Mean		
		Cc. per Min.	Sq. M.	Ml. per Min. per Sq. M.	Vol. per Cent	Liters per Min. per Sq. M.		Gm. per 100 Ml.	Gm. per 100 Ml.	Mm. Hg			Beats per Min.	Mm. H_2O
1	Before saline	43	1.79	116	2.3	5.0	32	9.8	5.8	155	80	110	100	5
	After 1,000 cc. saline	..	....	137	2.2	6.3	28	9.0	5.0	158	80	109	88	65
	66 min. later	..	....	106	2.8	3.8	29	9.2	5.3	150	76	103	84	30
2	Before saline	67	1.88	119	4.2	2.8	49	15.1	8.9	125	69	90	60	10
	After 1,000 cc. saline	..	....	110	3.3	3.2	45	13.9	7.8	124	66	85	57	40
	34 min. later	..	....	121	3.7	3.3	46	14.2	8.0	114	61	80	57	5
3	Before saline	53	1.77	157	3.9	4.0	43	12.9	6.4	106	62	78	82	35
	After 1,000 cc. saline	..	....	157	3.9	4.0	40	11.9	5.5	107	64	78	84	95
	45 min. later	..	....	147	4.5	3.3	42	12.2	5.8	113	70	83	84	50
4	Before saline	59	1.69	117	4.5	2.6	43	12.8	5.5	129	79	96	88	−15
	After 1,825 cc. saline	..	....	111	2.3	4.8	38	10.5	4.3	149	85	107	71	30
	35 min. later	..	....	134	3.8	3.5	39	11.4	4.8	143	88	109	79	− 5
5	Before saline	65	1.69	107	4.0	2.7	38	11.3	5.7	108	57	75	79	15
	After 1,300 cc. saline	..	....	116	3.3	3.5	33	9.6	4.6	116	62	84	75	45
	45 min. later	..	....	119	3.9	3.1	35	9.9	5.0	121	66	87	68	30
6	Before saline	77	1.82	134	2.7	4.9	45	14.1	6.6	106	60	76	68	50
	After 1,000 cc. saline	..	....	132	3.6	3.7	40	11.8	5.3	111	60	78	70	110
	28 min. later	..	....	126	3.2	4.0	42	12.9	6.1	109	60	79	68	65
7	Before saline	53	2.23	93	4.1	2.3	37	12.8	6.4	...	..	...	81	−25
	After 1,000 cc. saline	..	....	83	3.5	2.4	32	11.3	4.9	...	..	...	74	55
8	Before saline	59	1.81	142	3.4	4.2	41	12.7	6.4	...	..	...	104	5
	After 1,000 cc. saline	..	....	162	4.9	3.3	38	11.2	5.6	119	67	86	107	80
9	Before saline	67	1.64	104	4.2	2.5	35	9.8	7.3	122	78	...	75	−25
	15 min. after 1,000 cc. saline	..	....	130	4.1	3.2	30	8.5	5.1	...	..	...	68	70
	11 min. later	..	....	117	4.3	2.7	31	8.7	5.8	...	..	...	63	0
10	Before saline	62	1.75	130	4.6	2.9	34	10.9	5.8	112	60	77	62	− 5
	After 750 cc. saline	..	....	125	4.5	2.7	31	10.1	4.8	120	63	82	54	65
	35 min. later	..	....	138	5.4	2.6	34	10.7	5.1	...	..	...	57	15

variance of these findings from ours; in both, the cardiac output was determined by the method of right heart catheterization.

tion in the pulse rate.[10] The arterial pressure showed slight, apparently random, variations. Oxygen consumption and arterio-

TABLE II

NORMAL SUBJECTS RECEIVING 1,000 CC. OF 5 PER CENT HUMAN ALBUMIN IN PHYSIOLOGICAL SALINE SOLUTION

Patient	Remarks	Rate of Injection	Surface Area	Oxygen Consumption	A-V Oxygen Difference	Cardiac Index	Hematocrit Reading	Hemoglobin	Total Protein	Arterial Pressure			Pulse Rate	Atrial Pressure
										Systolic	Diastolic	Mean		
		Cc. per Min.	Sq. M.	Ml. per Min. per Sq. M.	Vol. per Cent	Liters per Min. per Sq. M.		Gm. per 100 Ml.	Gm. per 100 Ml.	Mm. Hg			Beats per Min.	Mm. H_2O
11	Before albumin.....	56	1.95	116	3.3	3.5	41	14.5	6.0	127	69	91	65	40
	After albumin.....	..	....	108	3.5	3.0	36	12.2	5.7	120	68	87	73	110
	70 min. later.....	..	....	133	3.3	4.0	39	12.7	5.9	...	..	...	...	75
12	Before albumin.....	63	1.69	151	3.5	4.3	45	....	5.9	110	65	81	100	15
	After albumin.....	..	....	170	3.7	4.6	37	....	5.6	113	65	80	103	120
13	Before albumin.....	63	1.61	117	3.4	3.4	34	10.0	7.2	136	78	98	94	−15
	After albumin.....	..	....	119	3.0	3.9	27	8.8	6.7	127	72	92	94	45
	55 min. later.....	..	....	137	3.0	4.6	28	8.9	6.8	140	80	100	84	15
14	Before albumin.....	32	2.0	127	3.6	3.6	46	14.2	6.8	125	75	88	88	−15
	After albumin.....	..	....	129	2.2	5.9	36	11.8	6.2	149	79	103	79	95
	55 min. later.....	..	....	111	2.5	4.4	39	12.6	6.5	155	79	103	60	+30
15	Before albumin.....	63	1.73	142	5.6	2.5	43	14.8	5.5	119	68	83	53	60
	After albumin.....	..	....	130	3.9	3.3	33	11.5	5.0	142	75	99	60	190
	60 min. later.....	..	....	124	4.0	3.1	37	13.8	5.6	142	78	98	52	90
16	Before albumin.....	37	1.73	129	4.2	3.1	38	12.7	5.9	163	86	113	66	20
	After albumin.....	..	....	121	2.4	5.1	29	10.0	5.5	166	84	113	66	90
	60 min. later.....	..	....	120	2.3	5.2	32	10.4	5.8	150	77	105	60	50
17	Before albumin.....	37	1.74	120	2.6	4.6	32	9.5	6.1	107	47	66	60	5
	After albumin.....	..	....	127	4.9	2.6	27	8.1	6.2	107	47	69	71	105
	100 min. later.....	..	....	118	...	...	..	7.8	6.4	...	..	...	...	45

The majority of the data given in this table appeared in an article on shock in the *Archives of Internal Medicine*, 77: 564, 1946.

The intravenous infusions produced little change in the pulse rate. This is in contrast to the effect of removing blood from the vascular system where the lowered atrial pressure is often accompanied by an elevavenous difference of mixed venous blood were not significantly altered.

In two patients x-ray studies of the transverse diameter of the heart were made with the patient in a horizontal position. Venous

tourniquets were applied to the thigh and inflated to the level of the diastolic pressure. After five minutes control films were taken. The venous tourniquets were released and the albumin solution was given rapidly. The average increase in blood volume produced by the albumin as calculated from the hematocrit readings was 1,000 cc. Repeat x-ray studies were made. From previous observations[10] it is known that the venous tourniquets lower the right atrial pressure an average of 45 mm., and the rapid administration of 1,000 cc. of 5 per cent albumin solution raises it an average of 80 mm. Thus, the change in right atrial pressure between the two sets of roentgenograms was approximately 125 mm. of water. No change in the size of the heart could be detected.

COMMENTS

The original stimulus to carry out the studies reported here was derived from observations on the hemodynamics of hemorrhage in man.[11] Hemorrhage causes first, a fall in atrial pressure and later a decrease in cardiac output and the clinical picture of shock. It soon became obvious that in the patients admitted with acute hemorrhage there was no absolute level of cardiac output at which the clinical symptoms of shock appeared. The absolute figure for cardiac index (output per sq. m. of surface area) had to be interpreted in the light of the requirements of the body for blood flow. A cardiac index of 3 might be adequate for one patient but grossly inadequate for another. The response to increasing the blood volume was used as a guide to determine whether the cardiac output was adequate. If a rise in atrial pressure caused a rise in cardiac output, it was believed that the increase in blood volume had been beneficial. This interpretation would not be valid if the cardiac output increased in normal subjects as the atrial pressure rose.

The evidence presented here, plus that obtained in the study of patients in shock, demonstrates that a rise in atrial pressure above the normal level will not consistently cause an increase in cardiac output. Hardy and Godfrey,[12] using the ballistocardiograph, found that the intravenous infusion of physiological saline solution caused an increase in cardiac output in patients who were dehydrated but produced no change in normally hydrated subjects. The important clinical implication is that a moderate increase in blood volume above the normal level in patients with shock will not place an added mechanical burden upon the heart. If factors are present which tend to cause fluid to localize in the lungs, the excess fluid may cause acute pulmonary edema even though heart failure does not occur.

Rather abrupt changes in the heart size are noted clinically in many conditions. Those occurring in patients with Addison's disease, arteriovenous fistula and following fever therapy are examples. Several explanations for these changes have been offered; one is that it is a reflection of a change in blood volume. The observations on heart size reported here demonstrate that an increase in blood volume of approximately 1 liter and a change in atrial pressure of approximately 125 mm. of water produce little change in the heart size of normal subjects. It must be remembered, however, that this increase in blood volume is not accompanied by a significant change in extracellular fluid volume.

The data reported here give further evidence that in normal subjects a large increase in blood volume causes no evidence of circulatory embarrassment. The most striking change was the rise in right atrial pressure. This is not interpreted as a sign of cardiac failure. The hearts in these subjects were normal and capable of large increases in cardiac output. If the fluids had induced heart failure, an actual fall in

cardiac output would have been expected. If the tone of the vascular bed is increased by sympatheticomimetic drugs, the pressure in the venous system will rise without any evidence of heart failure.[13] It appears that in normal subjects the elevation of venous pressure caused by increasing the blood volume or increasing the tone of the vascular bed cannot be interpreted as evidence of heart failure.

These experiments in normal subjects might at first sight appear to be at variance with common clinical experience in patients, particularly those with heart disease. Often in such patients intravenous infusions are not well tolerated and from time to time precipitate an attack of acute pulmonary edema. It is usually stated that the fluids, by raising the venous pressure, increase the work of the heart. The observation that raising the venous pressure fails to increase the output of a normal heart does not support such a belief. It appears probable that no increased burden of work is actually added to the heart. This concept is further supported by observations in this laboratory on venesection in two patients with chronic congestive failure. Sudden lowering of the venous pressure produced no fall in cardiac output. The clinical evidence still remains, however, that venesection may help and fluids may harm patients with cardiac failure. Other factors, therefore, must be operative.

It would appear that those factors responsible for the gradual development of pulmonary edema in the natural history of heart failure are responsible for the dramatic precipitation of the edema by the infusion. The patient with heart failure retains salt and water. This is another way of saying that the fluid intake exceeds the fluid output. A large portion of the retained salt and water accumulates in the lungs and is the primary factor in reducing the vital capacity. At this time it is not necessary to discuss the factors leading to the localization of fluid in the lungs; it is sufficient to emphasize that this localization of fluid is very common. When physiological saline solution is given intravenously at a rate which exceeds its excretion by the kidneys, those factors already tending to localize fluid in the lungs remain operative and a large portion of the added fluids pass into lungs already moderately edematous and cause an attack of frank pulmonary edema. Once the lungs have become sufficiently edematous, the final episode of severe dyspnea and production of frothy sputum may be accompanied by restlessness and anxiety, resulting in an increase in cardiac output and trapping of an additional few hundred cc. of blood behind an inadequate left ventricle.

These observations re-emphasize the fact that the rise in systemic venous pressure itself is not an important factor in producing dyspnea. The increase in venous pressure produced in normal subjects was much greater than those occurring in many cardiac patients who developed frank pulmonary edema from the intravenous administration of fluid. It has been demonstrated, however, that for a given rate of infusion the venous pressure may rise more rapidly in certain patients with cardiac failure than in normal subjects.[5] This is explained by several factors. The circulation in patients with cardiac failure may be inadequate although the patient is at rest; hence, the flow of blood to the tissues is diminished. They are less able to distribute the fluid throughout the body so that loss from the vascular system is delayed. In addition, such patients may already have sub-clinical retention of extracellular fluid; therefore, slight additions may completely fill the space normally available for the deposition of the injected fluid. Similarly, the blood volume may be somewhat increased before the infusion is begun even though the venous pressure is within normal limits. All of these

factors tend to result in a rapid increase in plasma volume when the infusion is started and the venous pressure may rise rapidly.

We believe that it is the fluid which leaves the blood stream and enters the lungs which causes the difficulty, and that a rise in venous pressure or a fall in the serum protein level is dangerous only when local factors in the lungs cause a disproportionate amount of the excess fluid to accumulate. The fact that the lungs are wet is an indication that certain factors are operative to cause a selective localization of retained fluid in the lungs. There is some additional clinical and experimental evidence to support this view. Dogs given large quantities of physiological saline develop massive generalized edema without obvious dyspnea.[14] Patients with nephrosis and cirrhosis develop marked edema without conspicuous pulmonary edema until heart failure intervenes. A patient with cardiac failure and an inadequate cardiac output who has dry lungs resulting from a regimen of salt restriction and administration of mercurial diuretics will tolerate intravenous fluids well. This same patient after a few days of a high salt diet may develop frank pulmonary edema during the administration of intravenous fluids.

Why does the fluid tend to accumulate in the lungs to such a striking degree in those patients with heart failure? If physiological saline solution is given to a normal subject at a rate which exceeds his ability to excrete fluid by the kidneys, many of the phenomena of congestive failure occur. He develops increased venous pressure and generalized edema but the early waterlogging of the lungs so characteristic of congestive failure is lacking. The hypothesis of left ventricular failure with an increase in pulmonary capillary pressure is still an attractive explanation to account for the difference in response of normal subjects and those with heart failure. If the pulmonary capillary pressure were increased above the normal level by damming back of blood behind the left ventricle it would explain why so much of retained salt and water accumulate in the lungs. If the pulmonary edema results from a high pulmonary capillary pressure plus retention of salt and water by the body, it would explain the observed facts that either causing the body to lose salt and water by the administration of diuretics or improving the circulation by the use of digitalis lessens the pulmonary congestion.

SUMMARY AND CONCLUSIONS

1. The effect of increasing the blood volume by the intravenous administration of 5 per cent albumin solution and physiological saline solution was studied.

2. The increase in blood volume consistently caused a rise in atrial pressure. The cardiac output, arterial blood pressure and pulse rate showed no consistent change.

3. Variations in atrial pressure of approximately 125 mm. of water produced no demonstrable change in the transverse diameter of the heart.

4. Increasing the blood volume and atrial pressure throws no demonstrable mechanical burden on the circulation in normal subjects. It is suggested that this may also be true in patients with heart failure. Acute pulmonary edema is precipitated by the intravenous administration of fluids in patients with heart failure because certain factors are operative to cause a large portion of the administered fluid to accumulate in lungs already moderately edematous.

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Value and Limitations of the Thymol Turbidity Test as an Index of Liver Disease*

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A NUMBER of reports have appeared in recent literature demonstrating the value of the thymol turbidity test in the diagnosis of liver disease.[1–7] A close correlation with the cephalin flocculation reaction was observed although certain definite discrepancies were noted.[4,5,8] The thymol turbidity test has the advantage of being extremely simple to perform and of furnishing accurate and reproducible values. Certain information has also been obtained regarding factors in the serum of patients with liver disease responsible for a positive reaction.[9–12] Serum lipids and lipoprotein complexes migrating electrophoretically in the beta globulin fraction were found to play an essential rôle in the reaction. The degree of elevation of the gamma globulin fraction was also found to be important. In acute infectious hepatitis values for the thymol turbidity test were found to reflect both the elevation in serum lipids and the increase in the globulin fraction.

The purpose of the present report is to present certain clinical observations on the value and limitations of the thymol turbidity test and to attempt to explain the results in terms of aberrations in the serum responsible for the reaction. Emphasis was placed on the study of results of the test in disease states which are characterized by a high globulin level of the serum.

In view of the observations previously reported[8] showing that maximal values for the thymol turbidity test may not be reached until after the acute symptomatic phase of infectious hepatitis is over, it was thought to be important to do serial determinations throughout the course of other diseases before drawing conclusions concerning the variation in thymol turbidity reaction. The results presented in this study represent the maximal aberrations found in various conditions as a result of serial determinations.

MATERIAL AND METHODS

The thymol turbidity test was carried out by the method of Maclagan[1] modified for the Coleman Jr. spectrophotometer.[2] The standard used was prepared as follows: 3 cc. of a $BaCl_2$ solution (containing 1.15 Gm. $BaCl_2.2H_2O$ per 100 cc.) is made to 100 cc. in a volumetric flask with 0.2 N H_2SO^4. This $BaSO_4$ suspension gives a turbidity equivalent to 20 units. By assigning the value 20 units to the optical density reading obtained in a colorimeter or a spectrophotometer at 650 mμ. with the $BaSO_4$ suspension, a standard curve can be constructed by drawing a line through the point obtained in the above manner and the 0 point on ordinary graph paper. The type of cuvette is not important as long as the same type is used for constructing the standard curve as for routine readings. This curve gives values somewhat higher than those found in other laboratories but, since the normal range was still found to be below 5 units, it was believed that the greater spread of values for positive sera aided in the interpretation of the results. Other liver function tests were performed in the manner described in a previous communication.[6] Determinations were carried out on the sera of patients admitted to the Outpatient Department and the Hospital of The Rockefeller Institute. A few patients in other hospitals in the New York area were also studied. Sera from certain patients with tropical diseases were obtained from various Army hospitals throughout the country.

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THE THYMOL TURBIDITY TEST IN DISEASES OF THE LIVER

Evidence that a positive thymol turbidity test is an indication of active liver disease was obtained from a study of the results of this test in infectious hepatitis. Table I shows observations on a group of Navy patients with acute infectious hepatitis who were admitted to The Rockefeller Institute Hospital within the first ten days of their illness. It can be seen that every one of these patients showed higher values for the thymol turbidity test than the highest value obtained in the normal control group.

TABLE I

COMPARISON OF THE RESULTS OF THYMOL TURBIDITY DETERMINATIONS IN CASES OF INFECTIOUS HEPATITIS AND IN NORMAL CONTROLS OF THE SAME AGE

No. of Cases	Maximal Values Reached during the Disease		
	Highest	Lowest	Average
76	41 units	8 units	23 units

No. of Cases	Values Obtained in Normal Individuals		
	Highest	Lowest	Average
46	5 units	0.5 units	3.0 units

The degree of elevation in acute hepatitis was variable and did not correspond to the severity of the illness. The data in Table II demonstrate that although the average maximal bilirubin values are usually proportional to the severity of clinical symptoms, the values for the thymol turbidity test show no such relationship. In fact, the group of patients exhibiting the most severe symptoms showed a slightly lower average maximal value for the thymol turbidity test than did patients in the other three groups with less severe symptoms of the disease. It appears, therefore, that although a positive reaction is associated with acute liver disease, the degree of turbidity is not a reflection of the severity of the liver damage.

In an investigation of a family epidemic of infectious hepatitis[5] opportunity was afforded to study several very mild nonicteric cases. The thymol turbidity test was found to be a more sensitive indicator of the presence of the disease than any other test that could be applied. In addition, it usually remained positive for at least six weeks enabling one to make the diagnosis several weeks after all other clinical and laboratory indications of the disease had disappeared. This served to emphasize the value of the test for epidemiologic surveys.

TABLE II

COMPARISON OF THE AVERAGE MAXIMAL VALUES OBTAINED DURING THE COURSE OF INFECTIOUS HEPATITIS FOR THE THYMOL TURBIDITY AND THE PLASMA BILIRUBIN IN PATIENTS GROUPED ACCORDING TO THE SEVERITY OF THE SYMPTOMS OF THE DISEASE

Severity of Symptoms	No. of Cases	Average Maximal Values Reached during the Course of the Disease	
		Bilirubin	Thymol Turbidity
++++	11	9.2	18.6
+++	22	8.5	24.0
++	18	4.6	23.0
+	16	3.2	19.0

The thymol turbidity test was also found to be of use in anticipating relapses of infectious hepatitis.[6] When serial determinations showed persistently high values during convalescence, the possibility of relapse could be strongly suspected and such patients could be returned to bed rest and dietary therapy before serious results ensued.

One of the chief uses of the thymol turbidity test was in the evaluation of mild, persistent symptoms following an attack of infectious hepatitis. The data of Table III show that in a group of service men observed more than six months after an attack of infectious hepatitis this test proved to be positive in 70 per cent of the men showing mild symptoms and in only 12 per cent of

the group who were symptom-free. It was positive more often than any other liver function test in this important group of patients who are so often diagnosed as psychoneurotic because the more commonly applied tests are negative. The other liver function tests and blood constituents studied in these patients, in addition to those shown in Table III, included the bilirubin excretion test, the prothrombin time, the hippuric acid excretion test, the urine urobilinogen, the serum albumin and globulin and the ratio of free to total plasma cholesterol.

TABLE III

VALUES FOR PLASMA BILIRUBIN, BROMSULFALEIN RETENTION, THE CEPHALIN FLOCCULATION REACTION AND THE THYMOL TURBIDITY REACTION IN PATIENTS SIX MONTHS OR MORE FOLLOWING AN ATTACK OF INFECTIOUS HEPATITIS

	No. of Cases	With Increased Plasma Bilirubin (Per Cent)	With Increased Bromsulfalein Retention (Per Cent)	With Positive Cephalin Flocculation Reaction (Per Cent)	With Increased Thymol Turbidity Values (Per Cent)
Persistent symptoms	40	45	48	50	70
No symptoms	34	15	0	12	12

TABLE IV

RESULTS OF THYMOL TURBIDITY TEST DETERMINATIONS IN PATIENTS WITH ALCOHOLIC AND NON-ALCOHOLIC CIRRHOSIS

	No. of Cases	Positive (Per Cent)	Highest Value, Units	Average Value, Units
Alcoholic cirrhosis	30	83	16	8.1
Non-alcoholic cirrhosis	24	96	36	16.7

In cirrhosis of the liver values for the thymol turbidity test proved to be considerably more variable than in infectious hepatitis. Table IV shows the results of this test in fifty-four patients with cirrhosis of the liver. The thymol turbidity test in patients whose liver disease was associated with chronic alcoholism and inadequate diet showed an average value of 8.1 units. Seventeen per cent of this group had normal values. These patients all had severe liver disease with definite alterations in the albumin and total globulin of the plasma. It is evident that this test does not give a true indication of the degree of liver involvement in these patients. The patients with cirrhosis of the liver who did not give a history of alcoholism showed a considerably higher average value for the thymol turbidity test. Five of the twenty-four patients in this group gave a definite history of infectious hepatitis in the past. In the remainder the etiology of the cirrhosis was obscure. Highest values were obtained in four cases of unusual cirrhosis associated with a globulin level of the serum above 6 Gm. per cent. Electrophoretic determinations demonstrated that the elevation in globulin was due entirely to an increase in the gamma globulin fraction.

THE THYMOL TURBIDITY TEST IN CONDITIONS OTHER THAN PRIMARY LIVER DISEASE

Table V summarizes the observations obtained in various disease states. For comparative purposes the value in normal patients and in those with liver disease were added. High values were found to be associated with the hyperglobulinemia found in various parasitic diseases, especially in kala azar. Here again the globulin aberration was almost entirely due to a rise in the gamma globulin fraction. In six patients with malaria that were studied a direct relation between the degree of elevation of values for the thymol turbidity test and the globulin level of the serum was present. This was also true in patients with typhus.

Serial determinations during the course of this disease revealed that values for the test showed a delayed rise and prolonged elevation which closely paralleled serum globulin changes. It appeared as if the thymol turbidity test merely reflected the globulin elevation in these acute infections.

TABLE V
COMPARISON OF MAXIMAL VALUES FOR THE THYMOL TURBIDITY TEST IN VARIOUS HEPATIC AND NON-HEPATIC DISEASES

	No. of Cases	Maximal Values Reached during the Disease	
		Highest	Average
Normal subjects	46	5.0	3.0
Infectious hepatitis	76	41	23.4
Alcoholic cirrhosis	30	16	8.1
Non-alcoholic cirrhosis	24	36	16.7
Kala azar	3	34	32.0
Typhus	6	16	12
Schistosomiasis	2	17	13
Malaria	6	19	15
Cinchophen poisoning	1	17	
CCl_4 poisoning	1	7	
Obstructive jaundice	6	7	3.8
Hemolytic jaundice	4	3	2.4
Rheumatoid arthritis	7	12	4.0
Rheumatic fever	10	8.5	5.9
Bacterial pneumonia	5	6.5	4.6
Atypical pneumonia	14	10 8	5.9
Multiple myeloma	3	5.0	4.0
Nephrosis	5	5.0	2.0

In certain chronic diseases, however, such as rheumatoid arthritis and multiple myeloma, values for the reaction did not correspond to the marked hyperglobulinemia that was present in some of these patients. The globulin level was above 7 Gm. per cent in each of the patients with multiple myeloma and strongly positive results for the Takata-Ara and formol-gel reactions were obtained whereas the thymol test was consistently negative. Electrophoretic analysis of one of these sera demonstrated that the globulin aberration was due to a marked increase in the gamma globulin fraction.

A limited number of observations were made on the use of the thymol turbidity test in the differentiation of obstructive and non-obstructive jaundice. Six jaundiced patients, who were later proven by operation or autopsy to have obstructive jaundice without histologic evidence of intrinsic parenchymal hepatic disease, all showed thymol turbidity values below 7 with an average value of 3.8 units. The lowest maximal value obtained in acute infectious hepatitis was 8 with an average of 23. It can be seen that this test alone may be of considerable value in differentiating the two conditions and when applied along with the alkaline phosphatase, cephalin flocculation and serum bilirubin, it becomes of particular value. Further observations are necessary to determine the effect of prolonged obstruction on the thymol turbidity reaction.

Four jaundiced patients who were later found to have familial hemolytic jaundice were sent to the Hospital of the Rockefeller Institute as cases of infectious hepatitis. The presence of normal values for the thymol turbidity test immediately initiated studies that led to the correct diagnosis.

Table V shows the average maximal values obtained during the course of three febrile diseases—rheumatic fever, pneumococcic pneumonia and atypical pneumonia. These patients showed a slight fall in the values for this test during convalescence. Atypical pneumonia was studied in considerable detail because an occasional patient showed values as high as 10 units during the early part of the disease.

Five patients with nephrosis and lipemic serum exhibited very high values for the thymol turbidity test as it is usually carried out. This was demonstrated to be a false positive reaction and by using a thymol solution with a high salt concentration in the control tube normal values for the test were obtained.[9]

RELATION OF THYMOL TURBIDITY TO CEPHALIN FLOCCULATION REACTION

Several observers[3,4,6,8,12] have pointed out differences between the thymol turbidity and the cephalin flocculation reactions although it is generally agreed that the two tests bear a close resemblance. Table VI

shows the comparative results of four liver function tests in a mild case of acute infectious hepatitis. This case was of special value because determinations were obtained prior to the acute onset and during the pre-icteric stage of the disease. The close relationship between the thymol turbidity and cephalin flocculation reactions during convalescence is readily apparent especially in contrast with the more rapid fall in the plasma bilirubin and bromsulfalein retention levels. In all of the cases of infectious hepatitis studied this close relationship existed. It was brought out quite strikingly in the patients demonstrating low abnormal values for the thymol turbidity test. These patients also showed negative or weakly positive results for the cephalin flocculation reaction despite the fact that they often were quite ill and markedly icteric. The main difference demonstrated by the two tests in the study of infectious hepatitis was that the cephalin flocculation test became positive several days earlier than did the thymol turbidity reaction. This can be clearly seen from the patient described in Table VI and was observed in all of five patients who were tested early in the pre-icteric stage of the disease. It may be concluded that the cephalin flocculation reaction is the more useful test during the pre-icteric stage of infectious hepatitis.

TABLE VI

COMPARISON OF SERIAL LIVER FUNCTION TEST DETERMINATIONS IN A MILD CASE OF ACUTE INFECTIOUS HEPATITIS OBSERVED DURING A FAMILY EPIDEMIC OF THE DISEASE

Day of Disease	Bilirubin (Mg. Per Cent)	Bromsulfalein Retention at 45 Minutes (Per Cent)	Thymol Turbidity	Cephalin Flocculation
12 days prior to onset	0.4	2	1	0
2	0.6	30	3	++
5	1.0	31	12	++
7	2.3	34	16	++
12	1.3	11	21	++
19	0.5	3	22	+++
27	0.6	1	15	++
34	0.4	2	13	++
48	0.35	1	7	0

Both the cephalin flocculation and the thymol turbidity tests showed a prolonged elevation during convalescence from infectious hepatitis after signs and symptoms of the disease had ended and values for other liver function tests had returned to normal. It was here that the two tests paralleled each other very closely. However, the thymol turbidity test usually showed a very slight elevation after the cephalin flocculation reaction had become negative.

Occasional patients with chronic hepatitis following acute infectious hepatitis showed definite differences in the behavior of the two tests. One patient who had marked symptoms of fatigue and liver tenderness always showed a negative cephalin flocculation reaction and a positive thymol turbidity reaction of more than 12 units in twenty-five simultaneous determinations over a period of one year. The reverse was also found in an occasional case but in general the thymol turbidity reaction was the more useful test in following the prolonged course of chronic hepatitis. (Table III.)

In cirrhosis of the liver the two tests also paralleled each other closely. Thirteen per cent of the alcoholic group of cirrhosis patients showed consistently negative cephalin flocculation reactions, as compared with 17 per cent for the thymol turbidity test. It is of significance that negative reactions for these two tests were usually found in the same patients although serum protein abnormalities were present. In general, the cephalin flocculation reaction was more definitely positive in the group of cirrhosis patients who showed only slight elevation of the thymol turbidity test values.

COMMENTS

The finding that 100 per cent of the patients with infectious hepatitis showed a higher maximal result for the thymol turbidity test than the highest value found in a normal control group demonstrates the value of this reaction for diagnosis of acute

liver damage. Its chief disadvantage, however, is that the intensity of the reaction is not an index to the severity of the liver damage.[1] This was also found to be true in patients with cirrhosis of the liver in whom the test proved to be of little value. The reaction is certainly not an estimate of the degree of aberration of liver function and should not be termed a liver function test. It is instead a sensitive indicator of acute liver damage. The degree of elevation in serum lipids and in the globulin fractions, which are the major components of the serum effecting a positive reaction, can hardly be considered indices of the degree of aberration of liver function. These components exhibit a delayed rise following acute liver damage, the exact significance of which is not clearly understood. It seems possible that these changes are related to the process of healing and regeneration of liver tissue and are therefore an indirect indication of acute damage.

The marked difference in values for the thymol turbidity test in alcoholic and non-alcoholic patients with cirrhosis of the liver is of some interest because it suggests a difference in the mechanism of causation of the cirrhosis. A majority of the patients in the non-alcoholic group showed marked hypergammaglobulinemia. The greater intensity of the thymol turbidity reaction in the non-alcoholic group of patients with cirrhosis reflected the more pronounced aberrations in gamma globulin in that group.

Some of the highest values for the thymol turbidity test were found in sera from patients with kala-azar in which there was extreme elevation of the gamma globulin fraction. Sera from patients with other parasitic diseases demonstrated an elevation of the thymol test which closely paralleled the elevation of total globulin. In these conditions there is evidence that the liver is involved. In malaria, for example, mild non-hemolytic jaundice is sometimes present and other liver function tests that do not depend on the globulin aberrations are positive.[13] The liver lesion in kala-azar is characterized by marked infiltration of inflammatory cells. Patients with unusual cirrhosis of the liver exhibiting extremely high gamma globulin and thymol turbidity values also showed a very marked cellular infiltration in the liver. The cellular reaction in the livers of patients with infectious hepatitis has often been described. In direct contrast, the hypergammaglobulinemia of multiple myeloma was not associated with a positive thymol turbidity reaction. Patients with cirrhosis of the liver following chronic alcoholism often showed elevation of the gamma globulin fraction in the presence of a negative thymol turbidity reaction. This was also true of patients with fatty livers. It was in the patients who exhibited a hyperglobulinemia associated with cellular infiltration of the liver that the thymol test correlated with the elevation in gamma globulin. These observations demonstrate that the test has some specificity and elevated values appear to be associated with those conditions in which an inflammatory process is present in the liver.

SUMMARY

In a group of seventy-six patients with infectious hepatitis who were followed throughout their illness the thymol turbidity test in every case showed a maximal value that was higher than the highest value obtained in a control group of forty-six patients. The results would appear to demonstrate the value of this reaction for the diagnosis of acute liver damage.

No correlation between severity of symptoms and degree of aberration in the thymol turbidity test could be found. The test proved to be of particular use in evaluating persistent symptoms following infectious hepatitis.

Patients with cirrhosis of the liver associated with chronic alcoholism showed considerably lower values for the thymol turbidity test than did patients in a non-alcoholic group. The test was of little value in estimating the degree of involvement of the liver in patients with cirrhosis.

Markedly positive reactions were associ-

ated with hyperglobulinemia in various parasitic diseases and other conditions in which an inflammatory process in the liver was present.

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Liver Function Tests in the Differential Diagnosis of Jaundice*

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IN a paper read before the 1946 Annual Meeting of the American Medical Association the author discussed the clinical diagnosis of jaundice with special attention to the value of data obtained from the history and physical examination of 100 patients.[1] The present paper is devoted to a discussion of the value of various laboratory tests in the differential diagnosis of jaundice and contains an analysis of 190 cases in which the diagnosis was definitely established by operation, autopsy or clinical course. (Table I.)

TABLE I
DISTRIBUTION OF CASES ACCORDING TO TYPES OF JAUNDICE

Obstructive Jaundice	
Common duct stone	39
Carcinoma of the pancreas	44
Lymphosarcoma	1
Stricture of the common duct	2
	86
Parenchymatous Jaundice	
Portal cirrhosis	42
Biliary cirrhosis	3
Xanthomatous biliary cirrhosis	1
Acute hepatitis	47
Drug toxicity	5
Acute yellow atrophy of the liver	3
Primary carcinoma of the liver	1
	102
Hemolytic Jaundice	
Congenital hemolytic icterus	2
Total	190

The conventional classification of jaundice into "hemolytic," "obstructive," and "parenchymatous" types according to the original cause of jaundice is followed in this paper.[2] The importance of making a differential diagnosis at least as to the type of jaundice present in a given patient lies in the fact that in cases of obstructive jaundice surgical operation for removal of the obstruction or for a palliative anastomosis of the gallbladder to the duodenum is the only effective treatment, whereas in cases of parenchymatous jaundice surgical treatment is useless and contraindicated.

In this discussion the emphasis is placed on the differentiation between obstructive and parenchymatous jaundice. Hemolytic jaundice is uncommon and patients suffering from chronic hemolytic icterus are not very ill so that operation on the biliary passages is rarely considered. In addition there are several laboratory findings which, in the aggregate, are characteristic of hemolytic jaundice. These findings are: An icteric index under 50 units, a normal amount of bile pigment in the stools, absence of bilirubin with the presence of large amounts of urobilinogen in the urine, "indirect" reaction with the qualitative Van den Bergh test, and an increased reticulocyte count in the blood.

Liver function tests can be divided into two classes. In the first class belong the so-called "excretory" tests in which a patent biliary system is necessary for the normal outcome of the test. An example of this class is the Rose Bengal dye excretion test. In the second class belong the so-called "metabolic" tests which are independent of the state of the bile passages. An example of this class is the galactose tolerance test.

* From the Division of Medicine, University of California Medical School, San Francisco, California. Read before the First Mexican Congress of Medicine, Mexico City, August 4–10, 1946.

In the differential diagnosis of jaundice we can rule out at once the use of all excretory liver function tests except the qualitative Van den Bergh test. The presence of jaundice indicates that the ability of the liver to excrete bilirubin is impaired and for this reason we cannot expect normal excretion of other substances such as dyes—used to estimate hepatic function—which must leave by way of the bile. Moreover, the fact that the liver is unable to excrete normally various substances is of no help in differential diagnosis because this may be due either to an extrahepatic block of the common bile duct or to pathologic changes in the hepatic cells.

The qualitative Van den Bergh test distinguishes between "indirect" bilirubin which enters the blood from the reticuloendothelial cells and "direct" bilirubin which enters the blood with the bile, having previously been excreted by the liver. In hemolytic jaundice which is caused by excessive hemolysis and overproduction of "indirect" bilirubin this test is of value because in most cases it gives the "indirect" reaction for many weeks after onset of jaundice. During the early stage of parenchymatous jaundice cloudy swelling of the hepatic cells diminishes the ability of the liver to take up "indirect" bilirubin which then accumulates in the blood. Later necrosis of some of the cells of the liver takes place leaving openings in the walls of the bile capillaries through which bile begins to enter the blood bringing with it "direct" bilirubin. Accordingly in the early stage of parenchymatous jaundice the Van den Bergh test gives the "indirect" reaction whereas later a mixed or "biphasic" reaction is the rule. In obstructive jaundice bile with "direct" bilirubin enters the blood from the first. Later as the back pressure of bile begins to injure the hepatic cells they are no longer able to take up normal amounts of "indirect" bilirubin and the latter also accumulates in the blood. Accordingly in obstructive jaundice the Van den Bergh test at first gives the "direct" reaction but later this is also changed to the "biphasic" type. For this reason the qualitative Van den Bergh test is useful for the differential diagnosis of jaundice only during the first week of jaundice, except in cases of hemolytic jaundice.

The principle underlying the use of metabolic liver function tests in the differential diagnosis of jaundice is that in obstruction of the common bile duct the hepatic parenchyma is usually intact whereas in various forms of acute or chronic hepatitis there are diffuse pathologic lesions in the hepatic cells resulting in more or less widespread necrosis. On the basis of this principle, in an ideal case we should with the use of any metabolic test get normal hepatic function in obstructive jaundice and impaired hepatic function in parenchymatous jaundice. However, these ideal conditions prevail only during the first few days after the onset of jaundice. Unfortunately, several days usually elapse before the patient or his family notice the yellow color of the sclerae and skin and then more time is lost because, unless pain is also present, jaundice apparently does not alarm most patients who often wait for weeks and sometimes months before seeking medical advice. As a result the back pressure of bile in obstructive jaundice causes damage to the hepatic cells and a week or at the most ten days after the obstruction becomes established most metabolic tests begin to register diminished function. In this way the usefulness of most of the metabolic liver function tests for the differential diagnosis of jaundice is lost soon after the onset of jaundice. Among the otherwise useful tests which in my experience are of little value for this purpose are the hippuric acid test, the cephalin flocculation test, determinations of total cholesterol, of alkaline phosphatase and of

urobilinogen in the urine according to the method of Wallace and Diamond.[3]

Fortunately there are two metabolic tests of liver function which enable the physician to distinguish between obstructive and parenchymatous jaundice in a large majority of cases. These tests are the intravenous galactose tolerance test and the response of prothrombin to vitamin K.

1. *The Intravenous Galactose Test.* The value of galactose in the differential diagnosis of jaundice lies in the observation that unlike most other functions of the liver the ability to metabolize galactose is impaired very little by obstructive jaundice of even several months' duration. In a previous paper[4] we called attention to the unreliable results obtained with the conventional oral galactose test which, in addition to the ability of the liver to metabolize galactose, is influenced by the rates of intestinal absorption and renal excretion of this sugar. At the same time the following method for doing the test was described:

After an oxalated blood sample has been obtained, a dose consisting of 1 cc. of a 50 per cent solution of galactose per kilogram of body weight is injected intravenously over a period of four to five minutes with a 100 cc. syringe with excentric tip, fitted with a short No. 19 gauge needle. Another oxalated blood sample is secured seventy-five minutes after the injection. Glucose is removed from the blood samples by fermentation with yeast according to Raymond and Blanco's[5] modification of Somogyi's method. The filtrates are analyzed for the non-fermentable reducing substance by the Hagedorn-Jensen method. In order to obtain the galactose content of the blood, the figure for reducing substances in the fasting blood is subtracted from the corresponding figure in the seventy-five-minute specimen. A correction of 24 per cent must be added if conversion tables for glucose are used. The details of the procedure and its adaptation to the Folin-Wu method have been described elsewhere.[6] The test is usually performed on the fasting patient, but in our experience such food as toast and coffee has produced no rise in the galactose level of the blood.

With this method almost all patients with obstructive jaundice of less than six months' duration had less than 20 mg. per cent of galactose in the blood seventy-five minutes after the injection of galactose while a large majority of patients with parenchymatous jaundice had more than 20 mg. of galactose in the blood.

In the present series all except one patient with uncomplicated obstructive jaundice due to stone in the common bile duct had less than 20 mg. per cent of galactose in the blood at the end of the test. In the one exception the blood galactose was 28 mg. per cent. Eight patients with choledocholithiasis and superimposed biliary cirrhosis had higher galactose values. All of the latter patients had a long history of repeated attacks of biliary colic associated with jaundice, chills and fever, so that it was easy to distinguish this group clinically from patients with uncomplicated obstructive jaundice. In all of these patients the clinical diagnosis of biliary cirrhosis was confirmed by operation and in half of them in addition by biopsy of the liver.

In all but three patients with uncomplicated obstructive jaundice due to carcinoma of the pancreas the blood galactose was under 20 mg. per cent. In the three exceptions the blood galactose was under 30 mg. per cent. Three patients with carcinoma of the pancreas had considerably higher values for galactose. Two of them also had cirrhosis of the liver as shown by operation and biopsy, and the third patient had massive metastatic growths in the liver. Two patients with jaundice due to benign postoperative stricture of the common duct had a normal galactose tolerance. Seven pa-

tients had obstructive jaundice from various causes longer than six months and in four of them considerable impairment of galactose tolerance was found.

In summary (Table II), practically all (95 per cent) patients with uncomplicated obstructive jaundice were diagnosed correctly by the intravenous galactose test. If we are to include in the group of obstructive jaundice the cases complicated by hepatic cirrhosis and the case with massive metastases to the liver, we still get a correct answer in 82 per cent of the cases. The mean galactose blood level of all patients with obstructive jaundice was 14 mg. per cent.

Seventy-six per cent of patients with cirrhosis of the liver had more than 20 mg. per cent of galactose in the blood. All but one of these patients had an icteric index over 50 units. Twenty-four per cent of patients with cirrhosis of the liver had less than 20 mg. per cent of galactose in the blood and all of them had an icteric index under 50 units. In addition to the mild degree of icterus which usually robs the case of urgency because surgical intervention is not contemplated, in most of the latter cases the presence of other signs pointing to parenchymatous hepatic disease such as ascites, "spider" angiomas and subcutaneous collateral circulation made the diagnosis clear.

Seventy-seven per cent of patients with acute hepatitis had a galactose blood level in excess of 20 mg. per cent. Twenty-three per cent had less than 20 mg. per cent of galactose in the blood. In the latter group, in all but three cases the hepatitis was mild (with an icteric index under 50 units) or of short duration and undergoing rapid improvement at the time the test was performed.

Three patients with acute yellow atrophy of the liver had a striking inability to metabolize galactose. Their blood galactose levels were 129, 139 and 145 mg. per cent. The highest figure for galactose in the blood observed by us in acute hepatitis with recovery was 116 mg. per cent and the highest figure obtained in cirrhosis of the liver was 92 mg. per cent. This limited experience suggests that galactose levels over 125 mg. per cent are of grave prognostic significance. This finding is of all the more value since in two of the three cases extremely high values for galactose were obtained by us before other indications of the gravity of the situation appeared and while the patients had

TABLE II

THE RESULTS OF THE INTRAVENOUS GALACTOSE TEST AND OF THE PROTHROMBIN RESPONSE TO VITAMIN K IN 188 PATIENTS WITH OBSTRUCTIVE OR PARENCHYMATOUS JAUNDICE

Type of Jaundice		No. of Cases	I.V. Galactose Test		Prothrombin Response to Vitamin K	
			Under 20 mg. (per cent)	Over 20 mg. (per cent)	Positive (per cent)	Negative (per cent)
Obstructive Jaundice	All cases*	86	82	18	91	9
	Uncomplicated cases	68	95	5		
Parenchymatous Jaundice	All cases†	102	24	76	4	96
	Cases with icteric index over 50 units	80	4	96		

* Including cases with biliary cirrhosis.

† Including cases with jaundice which was slight (icteric index under 50 units) or of short duration.

few subjective complaints. In one of these cases the outcome of the test was instrumental in bringing a close relative from a distant part of the country to the patient's bedside before death occurred.

Five patients with slight jaundice caused by toxic action of drugs (two cases due to cinchophen, two due to sulfonamides and one due to arsphenamine) were studied with the intravenous galactose test. Two of these patients had a galactose blood level of more than 20 mg. and three had a level of less than 20 mg. These results suggest that the galactose test is unreliable in the diagnosis of jaundice induced by drugs. However, this is not very important since a history of preceding medication with one of the hepatotoxic drugs is relatively easy to obtain.

In summary (Table II), 76 per cent of all patients with parenchymatous jaundice were identified correctly by means of the intravenous galactose test. Were we to exclude from our material patients with mild jaundice (with an icteric index under 50 units) or with jaundice lasting less than a week, the accuracy of the test in parenchymatous jaundice would rise to 96 per cent. The mean galactose level of the blood of all patients with parenchymatous jaundice was 56 mg. per cent. King and Aitken[7] as well as Maclagan[8] obtained comparable results with the intravenous galactose test. Combining the results of the intravenous galactose test in all cases of jaundice, it is seen that the outcome of the test alone made the differentiation between obstructive and parenchymatous jaundice in our series in three out of four cases. When certain simple additional clinical data are taken into consideration, it becomes possible to determine correctly the type of jaundice in almost all cases.

2. *Prothrombin Response to Vitamin K.* Maintenance of a normal prothrombin level in the plasma is one of the functions of the liver. This function can be fulfilled only in the presence of an adequate supply of vitamin K from the intestine. Obstructive jaundice lowers the prothrombin level by interfering with intestinal absorption of vitamin K and creating a vitamin K deficiency. Such a deficiency hypoprothrombinemia is corrected rapidly (often in six hours) by parenteral administration of vitamin K. Parenchymatous jaundice produces hypoprothrombinemia by interfering with the ability of the liver to form prothrombin. Consequently in the latter case administration of vitamin K either does not raise the prothrombin level at all or does so only slowly, and then the prothrombin level often decreases again in spite of continued administration of vitamin K. This difference, as has been repeatedly pointed out,[9–13] can be used for the differential diagnosis between obstructive and parenchymatous jaundice.

In the present study the prothrombin level was determined by the method of Quick.[14] The patient was then given an injection of 1 mg. of vitamin K* and the prothrombin determined again twenty-four to forty-eight hours later. Elevation of the prothrombin level was considered significant only if the original level was 70 per cent or less and the increase 20 per cent or more.

Among our patients with obstructive jaundice, 91 per cent responded with a significant increase of an initially low prothrombin concentration. Among those failing to respond, superimposed biliary cirrhosis, the presence of which was easy to determine from the history, accounted for one-half of the cases. Allen[15] also found that the presence of cholangitis with fever impaired the prothrombin response. In the group of our patients with parenchymatous jaundice, 96 per cent showed no increase in the prothrombin level. These figures indi-

* "Hykinone" ampules by Abbott Co. were used in this work but any other preparation of vitamin K suitable for parenteral administration can be employed.

cate a very satisfactory accuracy on the part of the prothrombin response to vitamin K in the differentiation of obstructive from parenchymatous types of jaundice. There was also excellent correlation between the results of the intravenous galactose test and the response of a low prothrombin level to vitamin K.

COMMENTS

In the diagnosis of diseases of the liver in general and in the differential diagnosis of jaundice in particular, liver function tests are an important diagnostic aid but they do not take the place of a good history or a careful physical examination. In many patients with jaundice the correct diagnosis can be made from the history and physical examination alone. In an additional number of cases ordinary laboratory studies and roentgenologic examinations will answer the question whether the jaundice is due to extrahepatic block and surgical intervention is necessary, or whether it is due to parenchymatous disease of the liver and medical treatment alone is indicated. Ordinary laboratory studies are particularly helpful in ruling out hemolytic jaundice. However, in most cases final recourse is made to liver function tests. It must be remembered that excretory liver function tests are useless in patients with jaundice. Among metabolic functions of the liver most decisive for the differentiation between obstructive and parenchymatous jaundice, in my experience, is the ability of the liver to metabolize galactose and to produce prothrombin following an injection of vitamin K. If these functions of the liver are not impaired or are impaired only slightly, the case is in the domain of the surgeon. If they are markedly impaired, the case is almost always strictly a medical problem. Although the results of either the intravenous galactose test or of the prothrombin response to vitamin K, especially if taken in conjunction with the history and physical findings, possess a high degree of accuracy for the differential diagnosis, it is advisable, whenever possible, to do both tests in every patient with jaundice.

Technically the galactose test is simple and after a little practice with galactose solutions of known concentration can be performed in any laboratory which is equipped to do blood sugar determinations. On the other hand, accurate prothrombin determinations are fairly difficult and reliable results usually require a larger laboratory where workers experienced in prothrombin determinations perform the tests.

SUMMARY

1. The pathologic physiology of different types of jaundice and its relation to "excretory" and "metabolic" liver function tests is discussed.

2. The results of the intravenous galactose test and of the response of prothrombin to vitamin K in the differential diagnosis of 190 patients with jaundice are analyzed.

3. The importance of distinguishing between obstructive jaundice for which surgical operation is the only effective treatment and parenchymatous jaundice which constitutes a strictly medical problem is pointed out.

4. The usefulness of the intravenous galactose test is demonstrated by the fact that, when taken alone, it made possible the differentiation between obstructive and parenchymatous jaundice in three out of four cases. When taken in conjunction with certain simple additional clinical data, this test allowed the identification of the type of jaundice in almost all cases.

5. The diagnostic accuracy of the prothrombin response to vitamin K is shown by the fact that it was present in nine of ten patients with obstructive jaundice and was absent in the same proportion of patients with parenchymatous jaundice.

CONCLUSIONS

1. Appropriate liver function tests are an important aid in the differential diagnosis of jaundice when taken in conjunction with data from the history, physical findings and ordinary laboratory studies.

2. With the help of the intravenous galactose test and the response of prothrombin to vitamin K it is possible to arrive at a correct diagnosis as to the type of jaundice in over 90 per cent of cases.

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Minimal Yet Adequate Program of Liver Function Studies in the Differential Diagnosis of Jaundice*

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THE problem of the differential diagnosis of jaundice, considered on the basis of the simplest possible classification (hemolytic, hepatocellular or obstructive), offers little difficulty with respect to identification of the first group, hemolytic jaundice. The enlarged spleen, reticulocytosis, spherocytosis and increased fragility of the red blood cells, the increased urobilinogenuria and hyperbilirubinemia to concentrations above that of the kidney threshold but with no bilirubin appearing in the urine, provide ample data for the diagnosis of congenital or acquired hemolytic icterus. Hepatocellular and obstructive jaundice present somewhat different problems. Although clinical differentiation between these two types of jaundice can frequently be made, it is often impossible to do so despite a carefully taken history and exhaustive physical examination. The age of the patient, pain, itching, the tint of the skin, weight loss and palpable spleen are signs and symptoms of statistical interest and value, but experience has shown that they often cannot be relied upon in making the differential diagnosis in the individual case. All too frequently patients with severe acute liver damage are subjected to the additional trauma of anesthesia and operation in an attempt to rule out extrahepatic obstruction. The hazards of undue delay in operation in cases of obstructive jaundice are well known.

The literature is replete with studies of liver function tests in jaundice, tests whose avowed purpose is to overcome these diagnostic uncertainties. Too often such studies concern themselves more with the establishment of the superiority of one test over another than with the development of a minimum yet adequate liver function study that will make possible differentiation between the two types of jaundice. The multiple functions of the liver and the known "dissociation" of the effects of hepatic damage upon these functions preclude the development of a single test that will serve such a purpose. Although the number of liver function tests that has been devised is legion and is constantly increasing, practicability dictates that only a few tests be used in any one study. In our experience we have found that a minimum yet adequate program can be developed if certain criteria are kept in mind. In addition to a reliable method for measuring the degree of icterus, such a program should include at least two tests which give positive results in obstructive jaundice and two whose results are positive in hepatocellular jaundice. The tests selected should evaluate different functions of the liver. By so doing, limitations imposed by the "dissociation" of effects of hepatic damage may be obviated.

In view of the dynamic character of liver function, especially in hepatocellular jaundice, tests for liver function should be per-

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formed as soon as jaundice is detected. Furthermore, because of the changing functional picture a real appreciation of what is occurring in the liver can be obtained only by repeating the tests at short intervals (preferably three or four days). To criticize the value of a test upon the basis of a single determination in a jaundiced patient betrays a lack of understanding of liver physiology. Thus, the variable intensity and duration of obstructive features in hepatocellular jaundice may give apparently misleading results in a single examination with a test which is affected primarily by obstruction in the biliary passages. Similarly, delay in applying the tests in the course of obstructive jaundice may result in the superposition of hepatocellular damage, producing what superficially appear to be false results in tests dependent upon hepatic cell damage. An appreciation of the mechanisms involved in the tests used, a proper combination of tests and their early and repeated use in jaundice usually give a feeling of assurance in the differential diagnosis of hepatocellular and obstructive jaundice which cannot be obtained by clinical observation alone. Moreover, the tests so used enable the clinician to follow the changing functional activity of the liver and permit an earlier and sounder prognosis.

Tests to Measure Intensity of Jaundice. Table 1 includes the liver function tests which we have found most useful in the study of jaundice. As a measure of the intensity of jaundice we found the quantitative van den Bergh test preferable to the icterus index. Since the color produced in the van den Bergh test results from a chemical reaction between bilirubin and Ehrlich's diazo reagent, errors can be avoided which may occur in the simple color matching of serum with the potassium dichromate standard used in determining the icterus index.

When laboratory facilities are very limited, the methylene blue test for "bilirubin" in the urine may serve as a useful although less accurate indicator of the course of icterus. This test was first described by Franke in 1931. He recommended that it be performed by the dropwise addition of a 0.2 per cent solution of methylene blue to

TABLE 1

TESTS RECOMMENDED FOR THE DIFFERENTIAL DIAGNOSIS OF OBSTRUCTIVE AND HEPATOCELLULAR JAUNDICE

1. Measurement of the Intensity of Jaundice
   a. Quantitative van den Bergh
   b. Icterus index
   c. Methylene blue test (urine)
2. Tests Affected Primarily by Hepatic Cell Damage; Function Tested
   a. Galactose tolerance test—carbohydrate metabolism
   b. Serum cholesterol esters (ester ratio)—lipid metabolism
   c. Cephalin cholesterol flocculation test—protein metabolism
   d. Colloidal gold test—protein metabolism
   e. Thymol turbidity test—protein metabolism
3. Tests Affected Primarily by Obstruction in the Biliary Passages
   a. Serum total cholesterol
   b. Serum phosphatase (alkaline)

5 cc. of urine. According to Franke,[1] in the presence of bilirubin the urine turns intensely green with the addition of the first drop of methylene blue. With additional methylene blue the specimen will become green, blue green and finally blue. The amount of methylene blue required to produce these color changes he believes is proportional to the quantity of bilirubin in the urine.

Myers[2] studied this test in employees who developed liver damage while working with tetrachlorethane. He found that the test became positive before the serum bilirubin concentration was elevated. As the jaundice disappeared the methylene blue test gave normal results when the serum bilirubin concentration was still above the kidney threshold level. In a recent issue of the Journal of the American Medical Association, Gellis and Stokes[3] found the test useful in evaluating the course of infectious hepatitis. They recommend the addition of two drops of a 0.2 per cent aqueous solution of methylene blue to 5 cc. of a pre-breakfast

urine specimen. If a green color results, more methylene blue is added dropwise and the last drop required to convert the green color to blue is recorded. Pipettes are used which deliver twenty drops of the solution per cc. (0.05 cc./drop). When readings are made by natural light, no difficulty is found in determining the change from green to blue. In a letter to the editor of the same issue of the Journal, Gellis, Neefe, Reinhold and Stokes[4] determine the final reading as one drop less than the number needed to produce the final color change. They regard the test as positive for bilirubin when more than four drops must be added. If more than five drops are required, the urine is diluted with distilled water and methylene blue is again added drop by drop until the end point is reached. Correction is made for the dilution factor. Dilution of the urine avoids difficulty in reading the end point. In accord with the results reported by Myers[2] in liver damage due to tetrachlorethane, Gellis and Stokes[3] found that the test may be positive in infectious hepatitis in the preicteric stage and negative in the recovery period when the icterus index is still elevated. They[3] believe the test can be of service in evaluating the course of the disease and in the prediction of impending relapse. The data in Figure 1, illustrating a case of infectious hepatitis with incomplete recovery and recrudescence, are in agreement with this view. (Fig. 1.)

The mechanism responsible for the color changes produced by the addition of methylene blue solution is not clear at present. Franke[1] believes it to be a specific reaction between methylene blue and bilirubin and that two drops of the methylene blue solution are equivalent to 0.1 mg. of bilirubin. Myers[2] does not share this opinion and attributes the green color in the reaction primarily to a mixture of the yellow and blue pigments. Reinhold[5] is in agreement with this, although he thinks that some chemical reaction occurs between methylene blue and bilirubin. Stokes, Gambill and Osterberg[6] conclude from spectrophotometric studies of methylene blue, sodium bilirubinate and their mixtures that the color reaction of the mixtures is dependent upon a blending of colors. Their conclusion is based upon the fact that the green solution of the mixtures gave two absorption bands, one of sodium bilirubinate and one of methylene blue, without producing any new band.

Gellis and Stokes[3] tested the pre-breakfast urine in 1000 patients with diseases other than hepatitis. In 74 per cent of the specimens, two drops of methylene blue solution produced a blue color, in 24.3 per cent, three drops and in 1.7 per cent, four drops were required. We have recently tested the pre-breakfast urine in 100 patients with functional and organic gastrointestinal disease other than liver disease. The final reading in fifty-six specimens was one drop, in thirty-five, two drops, three drops in eight and four drops in one.

Recording quantitative results in drops is frowned upon in many quarters. The variation in size of drops deliverable from a 1 cc. pipette, coupled with the effort necessary for the control of dropwise delivery, prompted us to use a 5 cc. burette set up for permanent use. When not in use, evaporation from the burette is prevented by a rubber stopper. The burette is graduated in 0.2 cc. units and is fitted with a micro dropper which permits fractionation of the drops. Normal urine (5 cc.) would, therefore, require 0.2 cc. or less of the methylene blue solution for production of a blue color. This modification in procedure may eliminate considerable error with urines of high "bilirubin" content that require considerable dilution.

Tests Affected Primarily by Hepatic Cell Damage. Of the tests designed to investigate the carbohydrate metabolism of the liver, the

galactose tolerance test alone has survived. Introduced by Bauer[7] in 1906, it came into general use in this country when one of us[8] showed its reliability if applied only to the differential diagnosis of obstructive and hepatocellular jaundice. It still remains one of the most useful tests for that purpose, especially when laboratory facilities are limited. In principle, the test is based upon the specific utilization of galactose by the liver. Under a test load of 40 Gm. of galactose administered orally to a normal individual after an overnight fast, 3 Gm. or less will be recovered in the urine in the ensuing five hours. The same results are obtained in cases of uncomplicated obstructive jaundice. In hepatocellular jaundice more than 3 Gm. are usually excreted in the five-hour period. Effective use of the galactose tolerance test, or any liver function test in which positive results are dependent upon acute diffuse parenchymal damage, can be made only if there is constant awareness of the dynamic state of liver function, as previously stated. (Fig. 2.)

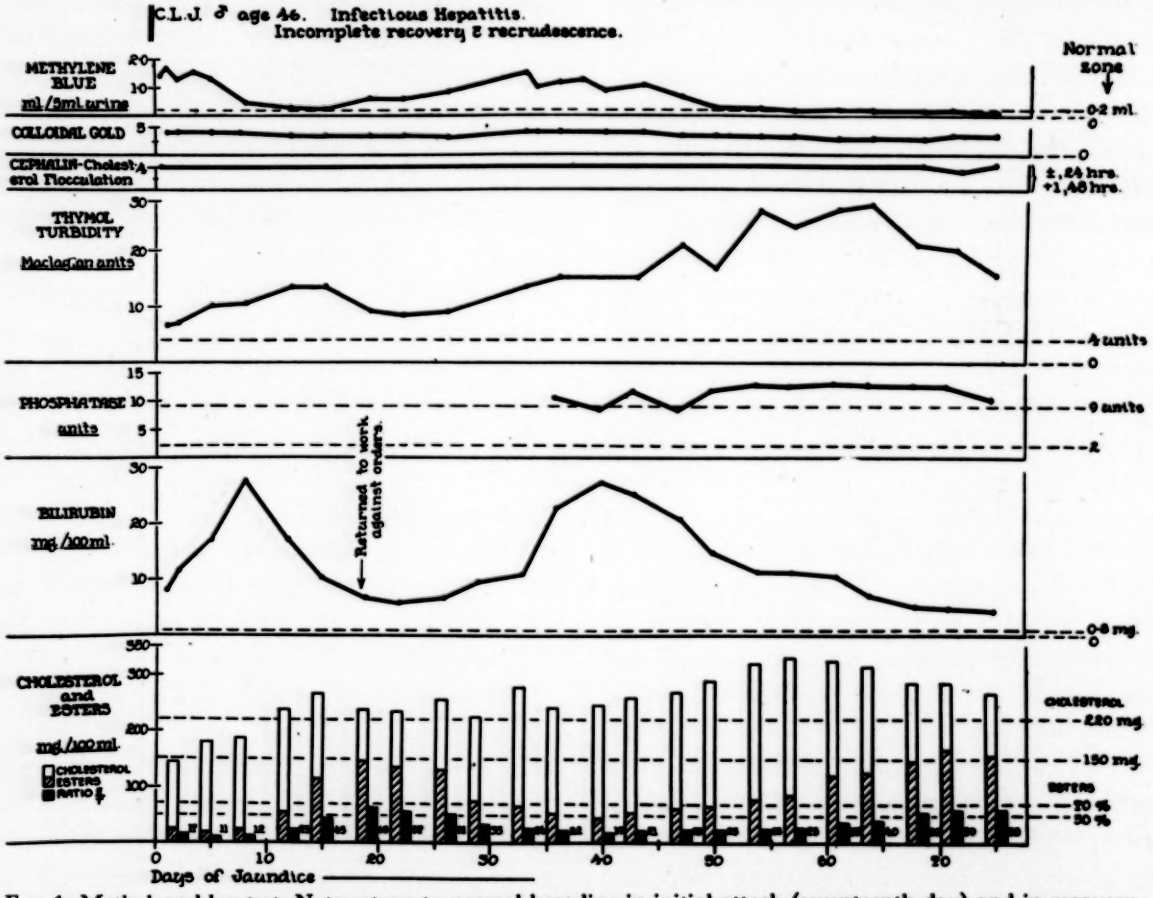

FIG. 1. Methylene blue test. Note return to normal base line in initial attack (seventeenth day) and in recovery following recrudescence (fiftieth day) while serum bilirubin levels were still well above the kidney threshold. The rise above values was the first indication of recrudescence of the disease and in this case this test was a more sensitive index of the change than was the drop in cholesterol ester ratio. It would be of interest to compare these two tests on the same days in very early cases or in pre-icteric stage of experimentally induced hepatitis. The rise of the cholesterol ester ratio to 63 per cent on the twentieth day, followed by the drop to 57 per cent on the twenty-third day and to 51 per cent on the twenty-seventh day we considered evidence of impending recrudescence even though no appreciable change in the serum bilirubin level had as yet occurred. The usual behavior of the cholesterol ester ratio in recovery from infectious hepatitis is shown in Figure 2 after the thirty-second day by the maintenance of the ratio near the upper limits of normal for some time into the recovery period. Recovery after recrudescence was slow and flocculation tests all remained abnormal after the cholesterol partition had returned to normal.

Cholesterol Partition. Serum cholesterol

partition and alkaline serum phosphatase have been discussed so fully in the literature that we shall limit ourselves to a consideration of a few essential details.[9] In normal blood serum, esterified cholesterol makes up 50 to 70 per cent of the total cholesterol. In obstructive jaundice there is usually a rise in total serum cholesterol. Esterification, however, keeps pace with this change, so that the percentage of cholesterol esters remains within the normal range. In hepatocellular jaundice there is generally no striking change in the total cholesterol concentration and esterification in the liver is impaired. This results in a lowering of the percentage of cholesterol esters in the blood, often to very low levels.

Since an appreciable increase in total cholesterol in jaundice is dependent upon biliary tract obstruction, and a low ester ratio is dependent upon acute diffuse hepatic cell damage, the cholesterol partition supplies two tests—one gives a positive result in obstructive and the other in hepatocellular jaundice. It is not only a very reliable procedure for the differential diagnosis of these two types of jaundice but when determined frequently during the course of

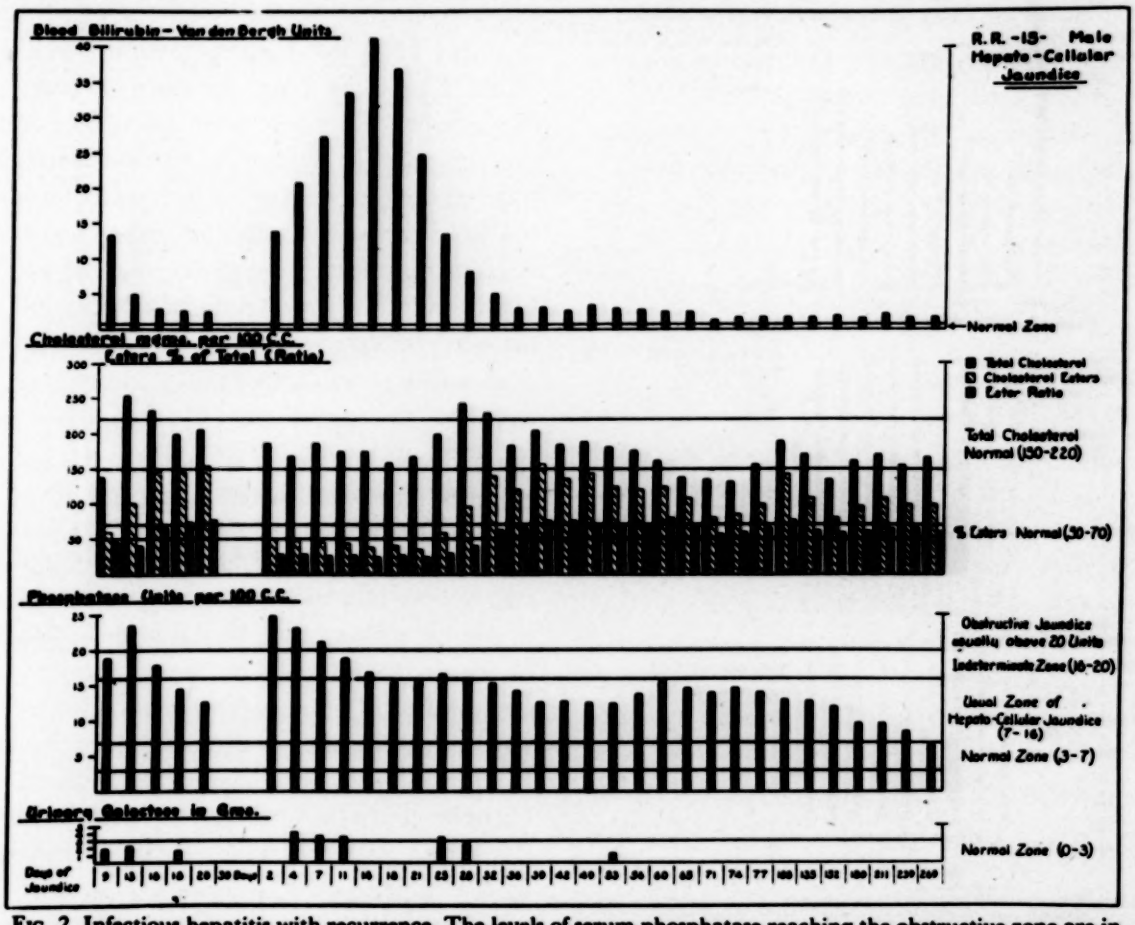

FIG. 2. Infectious hepatitis with recurrence. The levels of serum phosphatase reaching the obstructive zone are in this instance probably due to the higher values of phosphatase normally possible at this age level. The results with the galactose tolerance show the need for functional studies early in jaundice. In the first attack the disease was apparently very mild and the patient already in the recovery period when he entered the hospital on the ninth day of jaundice. Although the cholesterol ester ratio had not yet returned to normal, carbohydrate metabolism in the liver had recovered. In the recurrence, however, the galactose tolerance test was positive on the fourth day and remained so until the twenty-fifth day, but again returned to normal before the cholesterol ester ratio. This relationship of recovery is not always maintained. The need for application of liver function tests early in jaundice is obvious.

the disease it is also a dependable prognostic index in hepatocellular jaundice. The usual picture in recovery from this type of jaundice will show a moderate increase in total cholesterol and the percentage of esters will often hug the upper limits of normal. Especially significant is the fact that the esters will stay at a high normal level for some time. (Fig. 2, days 39 to 65.) Should the ester ratio consistently diminish shortly after normal values have been reached, recrudescence or recurrence of the disease may be suspected, even though the values for the ester ratio are still within normal limits. Figure 1 (days 20 to 30) illustrates this point. While making a very satisfactory recovery from an attack of infectious hepatitis, the patient decided, contrary to orders, to return to work on the twentieth day of jaundice when his serum bilirubin was still 6 mg. On that day his cholesterol esters comprised 63 per cent of the total serum cholesterol. On the twenty-third day his cholesterol esters had dropped to 57 per cent and on the twenty-seventh day to 51 per cent. While these were not striking changes and the readings were still within the normal zone we were convinced that the patient was having a recrudescence in spite of the fact that from the twentieth day to the twenty-seventh day there were no clinical manifestations or increase of serum bilirubin to suggest such a change. The subsequent course of the disease justified that opinion. It is especially interesting to note that the methylene blue test which had returned to normal on the thirteenth day had again become abnormal on the sixteenth day.

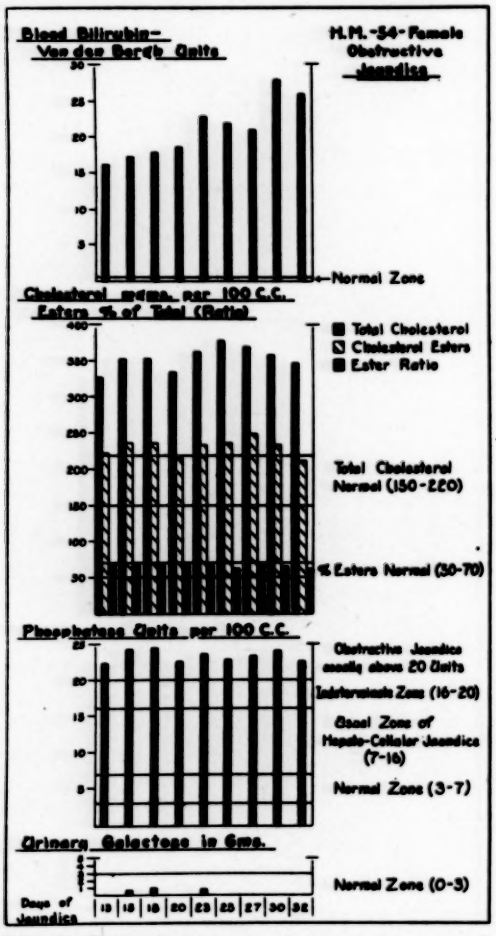

FIG. 3. Typical response of tests in a case of obstructive jaundice. Cause: carcinoma of head of pancreas.

Cephalin Cholesterol Flocculation. The flocculation tests are the most recent additions to the long list of liver function tests already in use in jaundice. The three tests in this group are (1) the Hanger cephalin cholesterol flocculation, (2) the colloidal gold and (3) the thymol turbidity tests. Of these the Hanger cephalin cholesterol flocculation is the oldest and has enjoyed the widest use. In 1938, Hanger[10] described a simple test for recognizing disturbances in the hepatic parenchyma, noting the capacity of blood serum in these cases to flocculate a colloidal suspension of a cephalin cholesterol complex. A negative test is one in which no flocculation occurs. A plus four reaction is one in which there is complete flocculation. Varying degrees of precipitation are recorded as+, ++, or +++. Flocculation is recorded at twenty-four and forty-eight hours and we consider as normal ± flocculation at the former and +1 at the latter period. Hanger[11] found no significant flocculation in twenty-five cases of obstructive jaundice. In thirty-three of thirty-eight cases

of hepatitis and cirrhosis he obtained a prompt flocculation. In a number of these patients tested repeatedly during the course of the disease he observed a close correlation between the clinical severity of the hepatic disorder and the degree of flocculation.

Kabat et al.[12] showed the gamma globulin fraction to be the sole component of the serum to give a positive cephalin cholesterol flocculation test. The concept at first entertained that flocculation was due to an alteration in the gamma globulin fraction[11] was discarded when these investigators found no difference in the flocculating power of the gamma globulin fraction obtained electrophoretically from normal sera (negative reaction) and that obtained from hepatitis sera (strongly positive). It was evident that the failure of normal sera to cause flocculation of the cephalin cholesterol complex was due to the inhibiting action of some component of the serum other than the gamma globulin. Moore et al.,[13] by the use of electrophoretically separated fractions of blood sera from normal people and from patients with hepatitis, found the flocculation-inhibiting action of the normal blood serum to be a function of the albumin fraction. On this basis, a positive flocculation could occur (1) if the gamma globulin fraction was increased, resulting in a relative decrease of albumin to a point insufficient to inhibit flocculation, (2) if a decrease in serum albumin occurs below the concentration at which it can inhibit flocculation, and (3) with a normal albumin level but a diminution in the flocculation-inhibiting power of the albumin fraction.

Colloidal Gold Test. Extensive studies on the mechanism of the colloidal gold reaction obtained with spinal fluid have related the type of reaction in pathologic conditions to variations in the balance between the precipitating activity of the globulin and the protective action of the albumin.[14] There is evidence that change in the individual globulin fractions, particularly in the euglobulin fraction, also plays an important rôle in the precipitation of colloidal gold.[15] The fact that similar changes in plasma protein fractions are frequently observed in hepatic damage prompted Gray[16] to apply the colloidal gold test to the study of liver disease. Maclagan[17] recently greatly simplified the method by reducing the procedure to a single tube technic. By rigorously controlling the reaction of the medium with buffer solutions, he was also able to obtain greater specificity with the test and more readily reproducible results. The degree of positivity is dependent upon the precipitation of gold and the extent of decolorization of the supernatant. The result is recorded as plus five when precipitation of the gold is complete and the supernatant is water-clear. A plus one is a reaction in which a slight turbidity occurs. A++, +++, or++++ is recorded with increasing precipitation and decolorization of the supernatant. Readings are made at the end of twenty-four hours. With the simplified method, Maclagan saw no positive readings with sera from normal subjects. With Gray's method Mateer et al.[18] reported a positive reaction in 10 per cent of the sera from normal subjects. Maclagan[17] suggested the use of the test for the differentiation of obstructive jaundice and infectious hepatitis and reported only two positive results in thirty-four cases of obstructive jaundice and five negative readings in 105 cases of infectious hepatitis. In arsenical jaundice (twenty-one of thirty-five cases) and in Weil's disease (eight of seventeen cases) he[17] found a much higher proportion of negative results than in infectious hepatitis.

Thymol Turbidity Test. In that delightful and charming little book, "The Way of an Investigator," which Cannon wrote shortly before he died, there is a chapter headed "Gains from Serendipity." The discovery and development of the thymol turbidity

test might be included as one of those gains. Serendipity, a word coined by Horace Walpole about the middle of the 18th century, had its origin in the title of an old fairy tale, "The Three Princes of Serendip" (former name of Ceylon), "the heroes of which were always making discoveries by accident and sagacity, of things they were not in quest of." In the discovery of the thymol turbidity test some accident but more sagacity was involved. Maclagan,[19] seeking to prevent the development of molds in the barbitone buffer which he employed for the colloidal gold reaction, added a crystal of thymol to the buffer solution. When the thymol-treated buffer solution was added to certain sera the mixture became turbid or a precipitate developed. The sera in which these changes occurred were all obtained from cases of parenchymatous liver disease. From this chance observation Maclagan developed the thymol turbidity test. The test consists of a simple mixture of blood serum with a saturated solution of thymol in a barbitone buffer of pH 7.8. He measures the degree of turbidity by comparing the solution after one-half hour with the turbidity of the formazin standards devised by Kingsbury and his associates.[20] These standards have been used for many years in the rough quantitative determination of protein in the urine. Normal sera give readings of 0 to 4 units, the number of units being the number of milligrams of protein represented by the standard matched, divided by ten, multiplied by the dilution of the blood serum. Maclagan[19] reported significantly positive values (above 4 units) in 120 of 130 cases of hepatitis and in only four of thirty-seven cases of obstructive jaundice. Watson and Rappaport[21] point out that the easy preparation of stable test solutions containing weighted amounts of pure chemicals, the completion of the test in one-half hour instead of the forty-eight hours necessary for the Hanger test and a simple method of measuring positivity, give the Maclagan test an advantage over the cephalin cholesterol flocculation.

Shank and Hoagland[22] recently reported a modification of the thymol turbidity standard which permits turbidimetric measurement in the spectrophotometer. The turbidity of a given reaction is expressed in units derived from a standard absorption curve prepared with barium sulfate suspensions. We have found a close correlation of the readings obtained in the same sera with Shank and Hoagland's method and the Kingsbury standards, except when the readings are very low (less than 2 units). At these levels the electrophotometric reading is certainly more accurate than tube matching with the Kingsbury standards. Since the levels at which the discrepancies occur are all within normal limits, the lack of close correlation of the two methods at these levels is not of practical importance.

In his original paper Maclagan[19] described the formation of a precipitate in positive tests when allowed to stand overnight. He apparently did not attach any special significance to these precipitates since he did not believe them to be an essential part of the reaction. In tests on seventy-six patients without demonstrable liver disease referred to later, we saw a precipitate in only one case on two occasions at eighteen hours with a reading of 2.5 and 2.8 units. This was in a severe iron deficiency anemia. We have, however, been impressed by the persistence of eighteen-hour precipitates for considerable periods after the half-hour readings have returned to normal in tests with sera from patients recovered from infectious hepatitis. We do not know the meaning of the persistent precipitate in the flocculation test at present. The continued production of some altered protein fraction or fractions of the blood serum after the other functions of the liver have been restored may be responsible. Such an

explanation appears plausible from the following studies on the disappearance of these precipitates in the reaction.

We attempted to quantitate the precipitate formed. To do so we read the turbidity photoelectrically one-half hour after the addition of the reagent and again at eighteen hours, after allowing the specimen to stand undisturbed at room temperature. These readings were expressed as a ratio and the turbidity of the supernatant at eighteen hours recorded as a percentage of the half hour turbidity reading.* The following table gives the results in a case of hepatitis in which the thymol turbidity reading returned to normal of 3.8 units on 5/9. Considerable precipitate had settled out at eighteen hours, since the turbidity of the supernatant was only 32 per cent of that of the half hour specimens. Table II shows the continued normal readings of the test in units and the gradual disappearance of precipitate at eighteen hours.

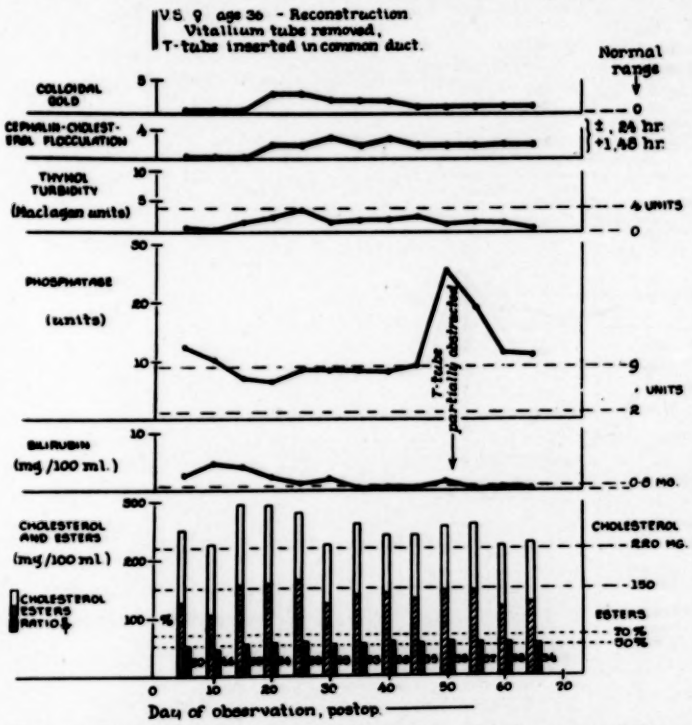

FIG. 4. Case of mild obstructive jaundice. The lesser sensitivity of the thymol turbidity test compared with that of the Hanger and colloidal gold tests actually gives it a greater specificity for the differentiation of obstructive and hepatocellular jaundice, as illustrated in this case of obstructive jaundice. The extreme sensitivity of the serum alkaline phosphatase concentration to obstruction in the biliary tract is shown by the sharp rise in its concentration when the T-tube became partially obstructed. The rise occurred with no significant change in serum bilirubin. In hepatocellular jaundice we consider the serum alkaline phosphatase level a measure of the degree of cholangiolar (Watson) jaundice present. The results of the very recent histochemical studies of Wachstein and Zak[36] of alkaline phosphatase in the liver in biliary obstruction support the view that the increase of serum phosphatase in liver damage is due to disturbed excretion of the enzyme.

The complete disappearance of precipitate at eighteen hours may indicate that the serum protein fractions have finally returned to normal and that the production of normal serum protein fractions by the liver is the last function to recover completely after acute diffuse hepatic damage.

* We have called this result the "18-Hour Turbidity Ratio."

The mechanism of the thymol turbidity test has not been established. Maclagan[19] studied the composition of the precipitate and found it to consist of a protein-thymol-phospholipid complex. He believes it probable that the protein is gamma globulin.

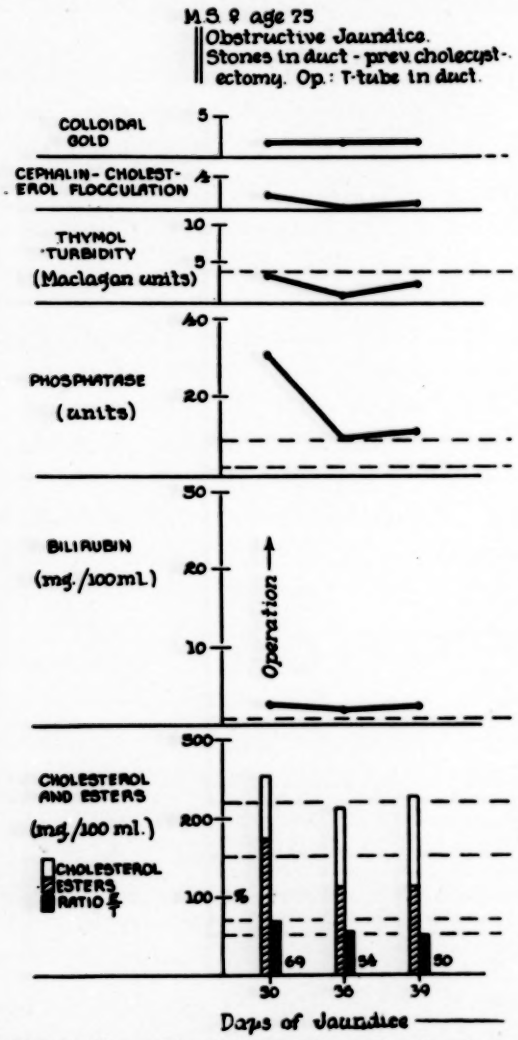

FIG. 5. Obstructive jaundice illustrating the sharp drop in serum phosphatase after bile drainage is established.

From a comparative study of the Hanger and Maclagan tests in liver disease, Watson and Rappaport[21] concluded that the underlying mechanism of the two tests is not identical.

In normal individuals very satisfactory results have been reported for all three flocculation tests. Hanger[11] reported only one positive result with the cephalin cholesterol flocculation in over 900 sera. Mateer et al.[18] obtained a normal response in all of forty healthy young doctors and nurses and Watson and Rappaport[21] in thirty-one presumably normal individuals.

With the simplified method for colloidal gold, Maclagan[17] found no positive reactions

TABLE II

Date 1946	Mg./% Serum Bilirubin	Units ½ Hr. Thymol Turbidity	Units 18 Hr. Supernatant	Percentage of Turbidity of Supernatant—18 Hr.
5/9		3.8	1.2	32
5/13		3.4	0.9	27
5/20		2.9	0.7	24
5/27		3.0	1.2	40
6/3		2.9	1.2	40
6/10		2.6	1.5	58
6/17		2.4	2.0	83
7/27		1.8	1.4	78

with sera from normal persons and in thirty-one normal individuals Watson and Rappaport[21] obtained readings below 4 units with the thymol turbidity test.

We considered it desirable to test the relative sensitivities of these three tests on sera from patients with gastrointestinal symptoms but with no discoverable liver disease. In seventy-six patients with functional or organic gastrointestinal disease other than liver disease, the cephalin cholesterol flocculation test was positive in seven (9.2 per cent). The colloidal gold test was positive in thirty-eight (50 per cent), in twenty of which the reading was +1. The thymol turbidity test was normal in all. Included among the seventy-six patients were fourteen cases of gallstone disease. These results suggest that the thymol turbidity test will probably have a greater specificity than the Hanger or colloidal gold test in the differential diagnosis of hepatocellular and obstructive jaundice. The data in Figures 4 and 5 indicate such a probability. These results also support the conclusion of Watson and Rappaport[21] that the underlying mechan-

isms responsible for the flocculation reactions are not identical.

Tests Affected Primarily by Obstruction in the Biliary Passages. Many investigators have confirmed the original report of Roberts[23] of an increase in the alkaline phosphatase activity of the blood in obstructive jaundice. The fact that relatively high readings may at times be observed in hepatocellular jaundice has created some doubt of the value of this test in icterus. Actually, when the alkaline phosphatase activity is studied serially in conjunction with the other tests suggested it helps to picture the shifting scene in the dynamic process of liver function. The effect of the variable and varying degree of canalicular obstruction (cholangiolar jaundice—Watson) that is present in practically all cases of hepatocellular jaundice will be mirrored in the changing serum phosphatase activity. Despite the failure of congenital atresia of the bile ducts to produce a rise in alkaline blood phosphatase, we have found the activity of this enzyme to be the most sensitive indicator of obstruction in the biliary passages. It is much more sensitive than changes in the serum bilirubin levels. (See effect of partial T-tube obstruction, Figure 4, or result of common duct drainage on phosphatase activity and serum bilirubin levels, Figure 5.)

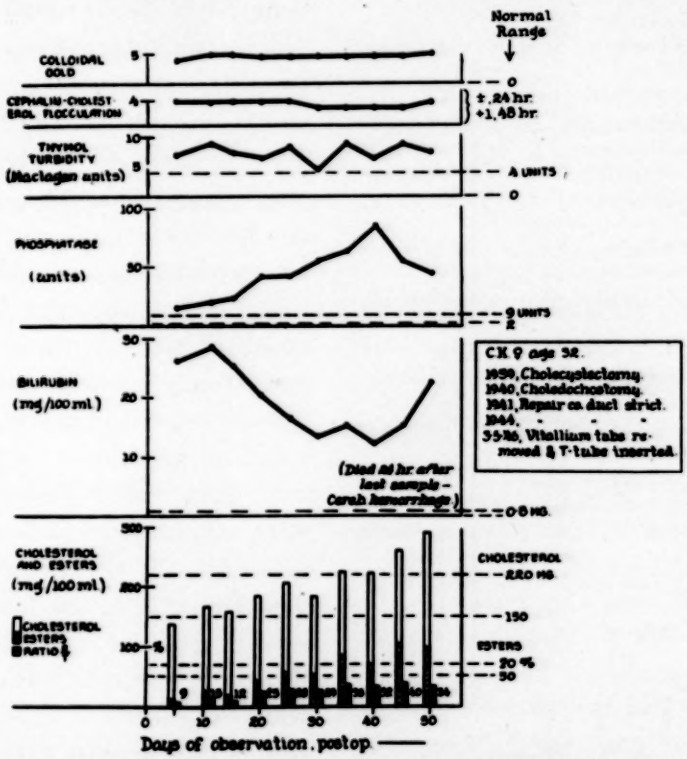

FIG. 6. Case in which multiple operations on the bilary tract had failed to cure jaundice. Exact duration of jaundice before last operation could not be determined. The results of liver function tests at this time showed that a severe degree of hepatic cell damage had developed. Such results of functional tests are a contraindication for surgery.

The increase in serum alkaline phosphatase seen in hepatic carcinoma, often in the absence of increased serum bilirubin, may be an expression of the striking sensitivity of the blood phosphatase concentration to obstruction. In such cases the growth may obstruct enough bile canaliculi to cause elevation of the phosphatase but may not involve sufficient bile channels to cause an increase in serum bilirubin. Another mechanism may be metastasis to the hilus nodes

with constriction of the common duct, sufficient to raise the pressure in the biliary tree to increase the blood phosphatase level but not the serum bilirubin level. Gutman, Olson, Gutman and Flood[24] have suggested that a rise in serum phosphatase in the absence of an increase in the serum bilirubin may be dependent upon the excretion of bile in the urine and the impermeability of the human kidney to phosphatase. The limitations imposed upon the use of the serum phosphatase level as an indicator of biliary tract obstruction by certain skeletal disorders and the increased and varying phosphatase level seen in the normal growing child are discussed in the very complete report of Gutman and his associates.[24]

TABLE III

TYPICAL RESULTS IN JAUNDICE WITH TESTS SUGGESTED

Obstructive Jaundice

1. Total serum cholesterol increased
2. Alkaline serum phosphatase increased considerably
3. Cholesterol ester ratio normal
4. Cephalin cholesterol flocculation normal. Not over ± at twenty-four hours nor more than +1 at forty-eight hours
5. Colloidal gold test (Maclagan) normal
6. Thymol turbidity test less than 4 units
7. Galactose tolerance normal; urinary output below 3 Gm.

Hepatocellular Jaundice

1. Total serum cholesterol normal or only moderately increased
2. Alkaline serum phosphatase normal or increased slightly
3. Cholesterol ester ratio decreased
4. Cephalin cholesterol flocculation more than ± at twenty-four hours, and more than +1 at forty-eight hours
5. Colloidal gold test (Maclagan) +1 to +5
6. Thymol turbidity test more than 4 units
7. Galactose tolerance—urinary output more than 3 Gm.

In a previous study of jaundice we[9] used the Kay-Roberts method for the determination of serum alkaline phosphatase. With that method the normal range for adults was 4 to 7 units. In hepatocellular jaundice we found that the serum alkaline phosphatase would generally remain below 15 units, while in obstructive jaundice a reading above 20 units was the usual finding. We have since changed to the Shinowara, Reinhart, Jones[25] technic, which gives results in modified Bodansky units, since the pH of the buffer is higher (pH 10.7) than the Bodansky buffer (pH 9.3). By this method the normal range for adults is 2 to 9 units. With this technic we have found that our readings for hepatocellular jaundice and for obstructive jaundice to fall in ranges similar to those which we obtained with the Kay-Roberts method.

CONCLUSIONS

If satisfactory laboratory facilities are available, we believe that a minimum yet adequate liver function study may be made in jaundice with the following tests: (1) quantitative van den Bergh, (2) serum cholesterol partition, (3) serum alkaline phosphatase, and (4) thymol turbidity (electrophotometrically).* This program, in addition to including the types and number of tests considered necessary in our opening discussion of the problem, has other advantages. All of the tests are made on the same sample of blood serum, thus assuring the same environmental conditions for the collection of the materials to be tested. The problem of nursing care, as regards the collection of test materials, is simplified and errors that may occur when multiple samples must be collected can be avoided. (Table III.)

We consider the above program the minimum procedure adequate for the study of jaundice. Should the physician have only very limited laboratory facilities available, he can still follow a case of jaundice with considerable confidence by combining (1) the methylene blue test, (2) the galactose tolerance test and (3) the thymol turbidity test. For these tests, pipettes, test tubes, a Bunsen burner and a set of Kingsbury standards will supply all the laboratory equip-

*Subsequent experience with the cephalin flocculation test has shown, however, that in homologous serum jaundice a positive test may be obtained in sera giving a negative reaction with the thymol turbidity test. Because of this it would seem advisble to include the cephalin flocculation test in the routine testing of sera.

ment necessary. Table III summarizes the characteristic results obtained in the two types of jaundice with the tests suggested, omitting those used to measure the intensity of icterus.

We are convinced that a judicious selection of liver function tests will clearly and almost invariably indicate the type of jaundice present. Applied *early* in the course of jaundice and repeated at short intervals (three to four days for a period of a week, i.e., three sets of readings) the tests indicated will usually permit identification of the type of jaundice. If such studies are continued at four to seven day intervals, a much sounder prognosis is possible than that gleaned from clinical observation alone. The investigator may thus take due cognizance of the multiplicity of liver functions, the "dissociation" of the effects of liver damage upon these functions and the dynamic quality of liver function, inadequate appreciation of which has led to so much unjustified criticism of liver function tests. Attempted evaluation of an isolated liver function test in jaundice is without meaning.

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"Blast Hypertension"

*Elevated Arterial Pressures in the Victims of the Texas City Disaster**

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DURING ministrations to the blast victims of the Texas City disaster we were struck by the high incidence of hypertension reaching, in extreme cases, systolic levels of 210 to 230 mm. and diastolic levels of 140 to 160 mm. Dr. E. J. Lefeber and other physicians working in the various city hospitals noted the same phenomenon. The finding of hypertension in the young, even in children, was particularly striking.

While hypertension resulting from physical or psychic trauma has been previously emphasized[1] and is usually interpreted as "neurogenic" in origin, World War II medical reports in American literature have failed to note an increased incidence of hypertension in the Armed Forces.[2] European observers, however, have recognized and reported this phenomenon.[3] The first of such reports appeared in 1943 from the Russian front where Gelshtein[3a] noted the presence of hypertension (over 140/85) in 12.3 per cent of front line troops with decreasing incidence in those further removed from the battle zone. Other Russian workers also observed the marked increase of severe, often deadly, but frequently reversible forms of "neurohypertension" in young individuals under war conditions.[3a] Later, Ehrstrom[3b] reported what he termed psychogenic "Kriegshypertonien" ("war hypertensions") from the Finnish front. He noted systolic hypertension of 150 mm. plus in 23 to 28 per cent of the front line soldiers; in more than one-half of these the diastolic pressure was also elevated. The less war-like the milieu, the lower was the incidence of hypertensive states, the least amount occurring in civilians not engaged in war work. Finally, among members of the armored brigade in the Western Desert campaign against Rommel, a diastolic "battle" pressure over 100 mm. was noted in 26.9 per cent and a systolic pressure of over 160 mm. in 38 per cent of the British soldiers studied. Of thirty-three diastolic hypertensive patients, twenty-eight reverted to normal pressures when re-examined two months later.[3c]

Many decades ago, Pavlov experimentally produced transient "neurogenic" hypertension by stimulating the sciatic nerve of a dog.[3a] Recently, prolonged and nearly continuous stimulation of the renal nerves of dogs by means of the sinusoidal current has been shown to produce more lasting hypertension.[4a] A closer reproduction of the Texas City blast hypertension is the successful maintenance of prolonged hypertension in the rat by repeated and nearly continuous air blasting.[4b]

OBSERVATIONS IN THE TEXAS CITY DISASTER

The docked ship Grandcamp, loaded with ammonium nitrate, exploded at 9:12 A.M., April 16, 1947. The nearby Monsanto Chemical plants, including the Styrene building, were next blasted apart at 9:15 A.M. It has been estimated that the force of the explosions approached that of the Bikini atom bomb. It is indeed remarkable that many people near the ship and the plants survived at all. Of 408 victims treated at the John Sealy Hospital on the day of the explosion, we studied 180 who had good

* From the Departments of Medicine and Pediatrics, University of Texas Medical School and the Heart Station of John Sealy Hospital, Galveston, Tex.

hospital records with frequently recorded blood pressures. These were bed patients suffering from contusions, lacerations, ruptured ear drums, simple and compound fractures and, in some instances, cerebral and visceral injuries. In many cases, but

TABLE I
AGE INCIDENCE OF THE 180 TEXAS CITY BLAST PATIENTS

Age	1–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	Unknown	Total
No.	2	20	47	57	20	16	8	4	6	180

not in all, the same nurse, doctor or medical student took most of the readings. We performed cold pressor tests on fifty-four of the still-hospitalized patients ten to thirteen days after the blasts. There were 148 men (thirty-two negro) and thirty-two women (four negro). The age incidence is shown in Table I; the majority were young men twenty to forty years of age. Past and family histories of hypertension and its complications, which are still being carefully gathered from the patients, their families and company records, were positive in less than 20 per cent of the total group. This was confirmed by the absence of even grade I retinal arteriosclerosis or electrocardiographic signs of left ventricular strain in the great majority of patients examined.

RESULTS

Table II classifies the highest levels of systolic and diastolic blood pressure reached in each of the 180 explosion victims at any time of their hospital stay. It will be noted that systolic pressures of 150 mm. and over were attained in 90 of the 180 patients. More noteworthy is the fact that diastolic hypertensive levels of 95 mm. and over occurred in 103, or more than one-half the patients; not infrequently (in 30 of the 103) without concomitant systolic hypertension. In only thirty-five were the diastolic pressures consistently below 86 mm.

For comparison we studied the records of one hundred consecutive patients, not blast victims, hospitalized on the surgical services in the two to three months preceding the disaster. It was a rather surprising fact that 34 per cent showed diastolic blood pressures of 95 mm. and over at one time or another. (Table III.) Although this percentage of hypertension was much

TABLE II
SYSTOLIC AND DIASTOLIC MAXIMA OF 180 VICTIMS OF THE TEXAS CITY EXPLOSIONS

	Systolic Pressure 150 mm. or More	Systolic Pressure 149 mm. or Less	Total
Diastolic pressure 95 mm. or more	73	30	103
Diastolic pressure 86–94 mm.	12	30	42
Diastolic pressure 85 mm. or less	5	30	35
Total	90	90	180

TABLE III
SYSTOLIC AND DIASTOLIC MAXIMA OF ONE-HUNDRED PATIENTS HOSPITALIZED ON THE SURGICAL SERVICES IN 1947

	Systolic Pressure 150 mm. or More	Systolic Pressure 149 mm. or Less	Total
Diastolic pressure 95 mm. or more	21	13	34
Diastolic pressure 86–94 mm.	2	48	50
Diastolic pressure 85 mm. or less	2	48	50
Total	25	75	100

TABLE IV
COLD PRESSOR TESTS IN FIFTY-FOUR HOSPITALIZED PATIENTS TEN TO THIRTEEN DAYS AFTER THE DISASTER

Postexplosion Diastolic Maxima	Positive (diastolic pressure, rise 17 mm. or more)	Borderline (diastolic pressure rise 14–16 mm.)	Negative (diastolic pressure rise 13 mm. or less)	Total
95 mm. or more	26	7	3	36
86–94 mm.	8	0	3	11
85 mm. or less	5	1	1	7
Total	39	8	7	54

below that of our blast patients (57 per cent), this may indicate that hypertensive agents, such as psychic and operative trauma, may operate in the general surgical group of patients.

In some blast victims, elevated blood pressures were found as early as one hour after the explosions; in others, they occurred postoperatively. This was so striking in isolated instances that we have made a preliminary study of fifty consecutive patients, not known hypertensives, operated upon on the surgical services in the same month as the blast victims. We found fourteen (28 per cent) showing temporary diastolic pressure rises to 95 mm. and over (as high as 120 mm.) and four others reaching 86 to 94 mm. Several showed high preoperative readings, possibly emotional in origin. Some blast victims likewise showed transient postoperative hypertension in previous hospital admissions.

The great majority of the blast victims, however, first presented hypertensive levels two to twenty-eight, generally seven to eight, hours after the explosions. (Figs. 1, 2 and 3.) In not a few patients admitted in various degrees of shock, the blood pressure rose, often to markedly supernormal levels, before returning to normal. In these patients, neither the administration of anti-shock drugs, nor of plasma, blood or other intravenous fluids (amounting often to 2 L. within several hours) appeared to influence the blood pressure curves. Following their use, the blood pressure varied too much to ascribe the hypertension to them. The length of the hypertensive state was very

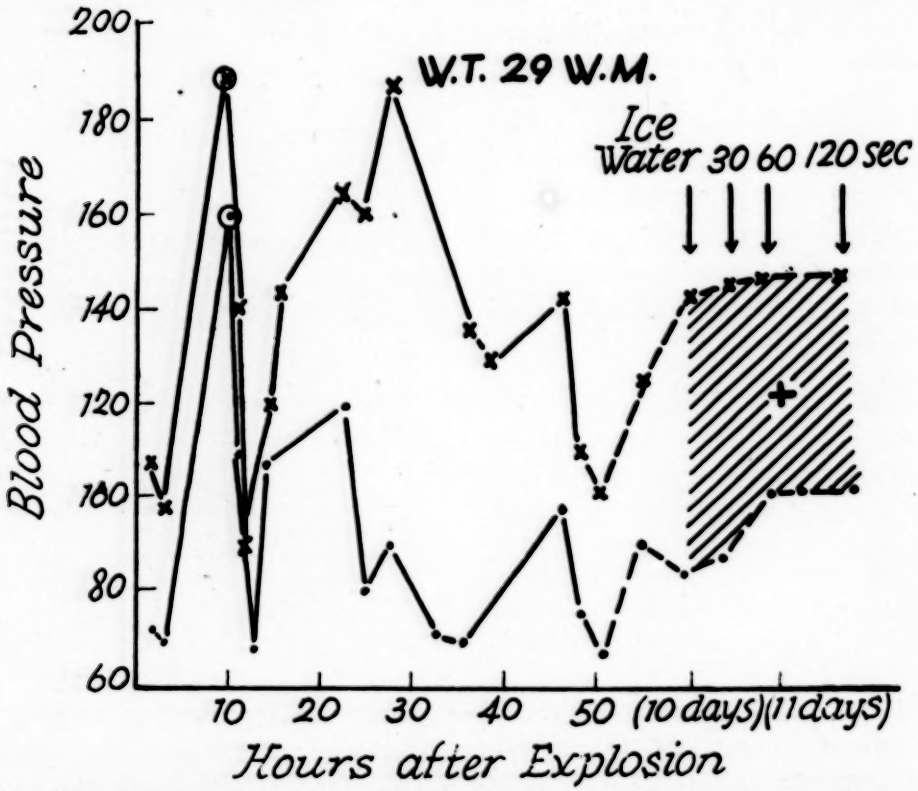

FIG. 1. W. T., twenty-nine, a white male, whose family and past histories were negative for hypertensive and allied states, was knocked down, without unconsciousness, on the ground floor of the Monsanto Office Building at the time it exploded and suffered multiple generalized lacerations with severance of the left ulnar nerve. He was given 32 mg. morphine and 1,000 cc. plasma and 1,000 cc. blood. Diastolic, 160 mm. ten hours after the blast; smaller rises occurred in the next few days. Eleven days later, blood pressure was 142/82, rising to 146/100 following immersion of forearm in ice water; the cold pressor test was positive.

variable in different individuals. The great majority presented several peaks of elevated arterial tension. They also showed generally normal blood pressures ten to fourteen days after the blasts although their cold pressor tests were usually positive of them suffered from relatively minor injuries.

Figure 4 shows the detailed maximal blood pressure responses of the entire group. At the top of the skew curves we find systolic blood pressure levels as high as

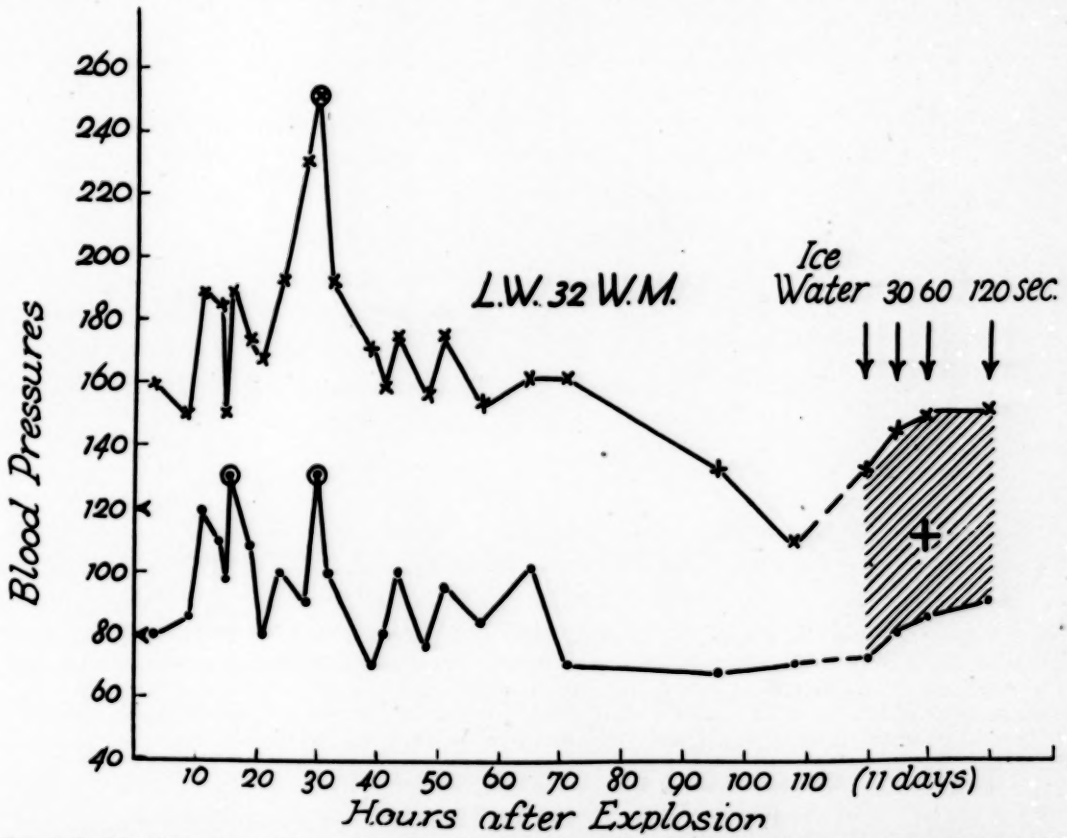

FIG. 2. L. W., thirty-two, white male, whose family and past histories were negative for hypertensive and allied states, was blown down, without unconsciousness, outside a warehouse 75 yards from the exploding ship. He sustained fractures of the left femur and right sixth and seventh ribs, with numerous lacerations. He was given 33 mg. morphine and 500 cc. plasma, 1,000 cc. 5 per cent glucose in saline during the first twenty-four hours. Systolic maximum pressure was 250 mm., diastolic 130 mm., thirty hours after the blast; smaller rises occurred before and after this time. Paroxysmal A-V nodal tachycardia was present five days after the explosions. The cold pressor test was positive (100/74, rising to 145/92) eleven days after the blast.

(Table IV) and minor diastolic elevations (around 90 mm.) were frequent at that time.

Whereas negroes presented diastolic reactions of 95 mm. plus in twenty-five of thirty-six cases, the corresponding figures for whites were 78 of 154 cases. This is of interest in connection with the well known high incidence of essential hypertension in the negro population. Women presented diastolic pressure readings of 95 mm. and over in fifteen of thirty-two patients; most 235 mm. and diastolic levels as high as 160 mm. Hg. Those patients showing the highest elevation of blood pressure did not have an appreciably greater incidence of positive past and family histories of hypertensive states than that of the total group. At the bottom of the skew curves, among the systolic levels of 110 to 130 and diastolic maxima of only 70 to 90 mm., are found many of those patients who succumbed to their injuries. Thus, three of twelve patients

with maximal diastolic values of 70 to 79 mm. died in shock despite huge quantities of intravenous fluids. If cases of severe fatal shock were subtracted from the total, the percentage of hypertensive states would be greater. Other subjects were false hypo-reactors in that their hypertensive phase may have been missed through infrequent blood pressure recordings.

From Table IV it is seen that we obtained positive cold pressor tests in thirty-nine of fifty-four patients until two weeks after the

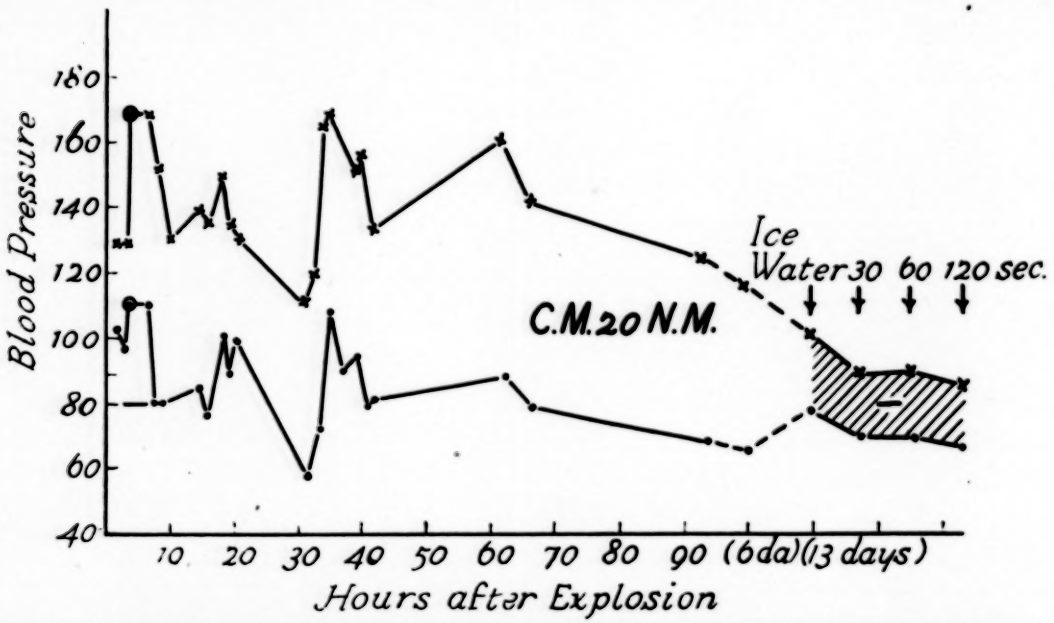

FIG. 3. C. M., twenty, negro male, whose family and past histories were negative for hypertension, had had low blood pressure according to company records. He was knocked unconscious for one-half hour as he was sitting 50 yards from exploding ship. He sustained compound comminuted fracture of the left femur, avulsion fracture of right ulnar styloid, multiple lacerations of arms and cerebral concussion (?). He received small amounts of morphine and fluids. The systolic maximum pressure was 172, diastolic 110, four hours after the blast; smaller rises occurred in the next few days. The cold pressor test was negative (100/75, falling to 85/65) thirteen days after the blast.

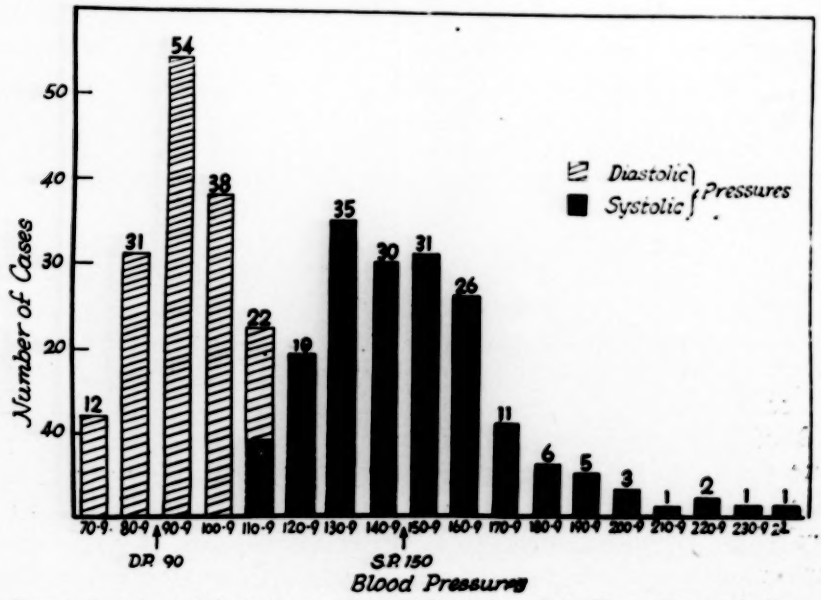

FIG. 4. Systolic and diastolic maxima of 180 victims of the Texas City explosions.

explosions. This is all the more significant since in the same fifty-four patients, thirty-six, or practically the same number, presented diastolic reactions of 95 mm. plus soon after the explosions. Likewise, while in seven patients the cold pressor tests were negative there were also seven patients that showed no diastolic hypertensive trend. However, as shown in Table IV, there was no parallelism between the hyper-reaction to ice water and the presumed hyper-reaction to the blast injuries. Thus, negative cold pressor tests were obtained in some patients showing high postexplosion diastolic pressures and vice versa.

Some examples of the actual cold pressor responses are shown in Figure 5. They emphasize, among other things, that the cold pressor responses do not mirror the height of the blood pressure obtained under other circumstances and that they may be negative with a positive family history and vice versa.

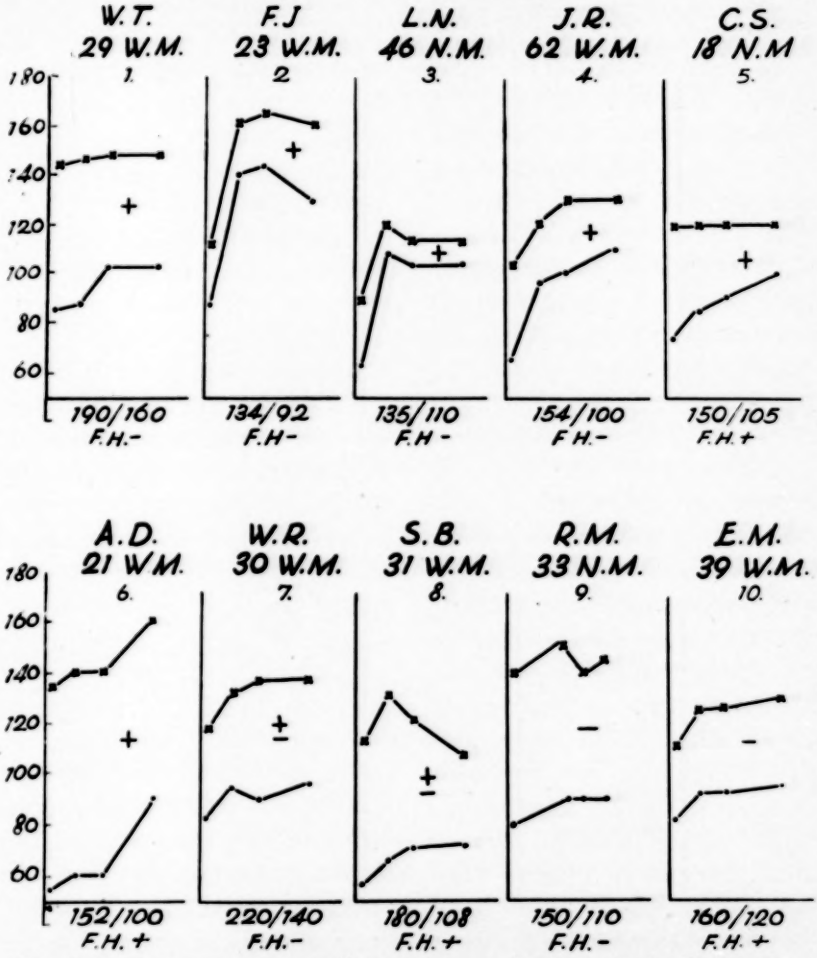

FIG. 5. Cold pressor responses of ten representative cases: six hyper-reactors, four with negative, two with positive, family histories (cases 1 to 6); two borderline reactors, one with negative, one with positive family histories (Cases 7 and 8); two hyporeactors, one with negative, one with positive family history of hypertension.

COMMENTS

Ehrstrom[3b] found a systolic hypertension of 150 mm. plus in 28 per cent of the Finnish soldiers hospitalized for various reasons and brought directly from the front battle lines. Our figure of 50 per cent (Table II) is higher, probably as a result of the relatively greater effects of the blasts on our patients. For the same reason our hypertensive incidence is higher than that which Gelshtein[3a] gives

for the Russian front line troops. At first we attempted to correlate the hypertensive reactions with the crudely classified degrees of physical injury that our patients suffered. We failed to do so. All we can say is that at the State Psychiatric Hospital, where some minor casualties were seen and quickly dismissed, diastolic hypertension of 95 mm. plus (100 mm.) was noted in only one of twelve thoroughly documented, and of thirty-six total cases. It was also our impression that patients, many of them women, slightly injured in their homes and far removed from the blast area helped to swell the hyporeactor group. On the other hand, many patients with simple contusions and lacerations were among those with the most marked systolic and diastolic elevations.

Neuropsychiatric Factors. Intracranial injuries, which if one can judge from the great frequency of draining ears[5] and confused states, were probably more prevalent than the absence of focal neurologic signs or x-ray evidences of skull fractures would indicate, must be considered in the etiology of the postexplosion hypertensive state in our patients. While traumatic cortical lesions, subarachnoid and intraventricular hemorrhage and other intracranial conditions have been blamed for "neurogenic" hypertension,[1a] their existence in our patients is problematic except in a few seriously injured patients, several of whom died without any hypertensive phase at all.

"Neurogenic" hypertension resulting from pain (as in one of our patients with a severe burn showing fairly continuous distress and hypertension) or great fear or anxiety, is rendered less likely by the remarkable stoicism of the victims in the first few days following the disaster and the routine use of morphine and paraldehyde. Unrelieved anoxia, asphyxia (as from respiratory obstruction) or marked restlessness were not present in more than a few of our patients. That "neurogenic" hypertension can occur even in uninjured front line soldiers,[3] as well as in students before examinations,[3b] cannot be denied. Can it reach the levels that were shown in a few of our patients? Fishberg[6] quotes Otto Mueller's case of "psychogenic" hypertension of 280 mm. systolic, followed after successful settlement of the mental conflict by years of normal blood pressure.

Renal Factors. Involvement of the kidneys apparently played a minor rôle in our patients. One patient in the series with renal trauma and hematuria did present a hypertensive phase. Hypertension in traumatized kidneys is not frequent, however.[7a] It is conceivable, on the other hand, that those patients who passed through a shock phase had developed, as a result of decreased renal pulse pressure, various circulating vasoconstrictor substances.[7b,c] How are they, as other hormonal substances suggested below, to explain the continuous and rapid fluctuations of blood pressure from hypertensive to normal or hypotensive levels seen in many of our patients? Patients with prolonged shock were very infrequent in number and they usually died without any hypertensive phase at all. Patients demonstrating anuria, oliguria, hemoconcentration or urinary abnormalities were likewise rare. Only one patient, presenting terminal slight hypertension (146/100), died in uremia, presumably the result of "crush injury" of the pelvis; this was the only patient who showed azotemia of any degree. No other cases of ischemic muscle necrosis with renal insufficiency and hypertension[7d] developed in our series. However, "psychogenic vasoconstriction of the kidney," not excluding emotional hyperadrenalemia as a cause and resulting in a fall in the renal blood flow of as much as 40 per cent,[7e] could easily give rise to vasoconstrictor substances originating in the temporarily ischemic kidneys.

Adrenal Factors. The rôle of the adrenal glands must always be considered in traumatic cases. Epinephrine secretion, accompanied by a rise in blood pressure and heart rate, staring pupils, pallor, etc., was considered the main factor in the "alarm reaction" by Cannon[8a] and in "battle" hypertension of the British troops in Africa

by Graham.[3c] Transient hyperadrenalemia could easily play a part in the general sympathetic overactivity in our patients but would account mainly for elevation of systolic pressures.

Arteriolar vasoconstriction, from whatever cause, certainly exceeded increased cardiac output among the compensatory phenomena inasmuch as diastolic hypertension occurred more commonly than, and often independent of, systolic hypertension. In general, marked compensatory hypertension was prognostic of survival and failure of vasoconstriction, as evidenced by constant low diastolic pressures, frequently led to death in our shocked patients. The finding of hypotension, normotension and hypertension in all degrees and proportions in many patients who presented the clinical picture of traumatic shock corroborates the experimental and clinical evidence pointing to lack of consistent hypotension in surgical shock except in its terminal or irreversible phases.[9] As clinical shock was present in only a portion of the series, it cannot of itself be held accountable for the more generally prevalent hypertensive states.

Selye[8b] has recently proposed that in the "resistance phase" of the "adaptation syndrome" to "noxious stimuli," the rise in blood pressure, sometimes to hypernormal levels, results from adrenal cortical oversecretion in animals. Such a theory, if true, would explain the finding of hypertension following shock in some of our patients. Hypervolemia and hypertension have been demonstrated in human subjects following the use of desoxycorticosterone.[8c] There is no direct proof at present that such a compensatory phenomenon occurs in human subjects following traumatic shock.

Significance of Cold Pressure Tests. The results of the cold pressor tests, even if markedly positive, speak neither for familial predisposition nor for the neurogenic or hormonal mechanism of hypertension in our subjects. Cold, being considered a "noxious stimulus," stimulates not only the sympathetic nervous system but also the adrenal glands and, presumably through producing renal ischemia, can evoke vasoconstrictor substances from the kidney as well. The highest percentage of hyper-reactors in the general population is placed at 18 per cent by Hines[10a] and 56.7 per cent (at sixty to sixty-nine years of age) by Russek and Zohman.[10b] These figures are greatly exceeded by those of our patients. Will our patients hyper-react as much in the future? Russek[10b] and Todd[10c] among others have disproven the idea that a positive cold pressor test indicates either a positive family history or future hypertension. Why may it not mean, as in our patients, vascular over-reaction to cold as to other noxae through the medium of a temporarily hypersensitive sympathetic nervous system and, perhaps, transiently formed hormonal vasoconstrictors?

Whether the hypertensive states shown by the blast victims represent actual or latent essential hypertension cannot be affirmed or denied on the basis of our data. Future studies of our group, as well as the groups of soldiers studied abroad, are badly needed. Master,[11a] in re-examining a group of sixty navy personnel who had shown a single reading of 140-156/77-90 from one to seven years previously, found hypertension in 74 per cent, with diastolic pressures over 100 mm. in 25 per cent. Garai[11b] found positive cold pressor tests in twelve of fifteen shipwrecked seamen several months to one to two years after their ships had been sunk by torpedoes or mines. Controls showed positive cold pressor tests in less than one-half the patients. In our experience, as in Garai's, cold hyper-reactors are particularly common among psychoneurotic individuals.

SUMMARY

Careful observations show definite although not prolonged diastolic hypertension in the majority of the victims of the Texas City disaster. We intend to follow-up our patients and report on them in the future.

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Coexisting Auricular Fibrillation and Complete Heart Block

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A FEW isolated reports of patients with conditions of auricular fibrillation coexisting with complete heart block have appeared in the literature, but so far as we know, no attempt has been made to analyze a group of such cases in search of clinical or pathologic features which they may share in common. Our curiosity was aroused particularly in finding that this combination is not especially rare.

During 1943 to 1945, inclusive, a total of ten patients at the Mayo Clinic were found to have definite electrocardiographic findings of concomitant auricular fibrillation and complete auriculoventricular dissociation. In reviewing the electrocardiographic files two instances of coexisting auricular flutter and complete heart block were also encountered but are not included in this analysis.

The concurrence of these two cardiac irregularities is disclosed electrocardiographically by the following criteria: (1) a *regular*, slow ventricular rate (usually less than 65 beats per minute); (2) absent P waves and (3) the presence of "fibrillary waves." Conversely, if complete heart block is not present with auricular fibrillation the ventricles will exhibit irregularity in rhythm; namely, the R-R intervals will not be equidistant, and the rate tends to be more rapid.

Ashman and Hull have stated that the complete heart block in this combination "is usually functional rather than due to any organic lesion." It may, of course, be purely a digitalis effect in some cases, as will be shown presently, but it is very doubtful that any of our cases were on a so-called functional basis because in every instance there was apparent severe myocardial damage incident to either arteriosclerosis, rheumatic endocarditis or hypertension.

Because of the rarity of auricular fibrillation in children the combination of auricular fibrillation and complete heart block probably occurs exclusively in adults. So far as we know, no cases of this combination in children have been reported.

ANALYSIS OF CASES

Of the ten patients studied seven were men. The youngest patient was a man of forty-three years; the oldest who was seventy-eight years, also was a man. The average age was sixty-two years. All patients had roentgenographic evidence of marked cardiac enlargement, and similarly all had diagnoses of serious cardiac or cardiovascular disease as follows: rheumatic heart disease, four cases; hypertensive and coronary heart disease, six cases. Severe arteriosclerosis was noted in two cases. Of the hypertensive group two gave a past history of cerebrovascular accident. Seven patients either had a past history of congestive failure or were decompensated when seen at the clinic. Varying degrees of dyspnea had been experienced in all cases but one.

In three cases the complete auriculoventricular dissociation was undoubtedly due

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to a digitalis effect, which does not in itself imply digitalis intoxication.

To date there have been two deaths. One death occurred following a transurethral resection, from causes unrelated to the heart. The other patient died elsewhere about seven months after dismissal from the clinic and a necrospy was not performed. The cardiac findings at necropsy in the first of these two cases (Case VIII) were as follows: (1) patent foramen ovale (4.0 by 3.0 cm.) with hypertrophy of the right auricle, grade 2 (on the basis of 1 to 4 in which 1 represents the mildest and 4 the most severe condition); pulmonary arteriosclerosis, grade 1, and dilatation; (2) healed rheumatic mitral and aortic endocarditis with calcification; (3) hypertrophy of the heart; weight 520 Gm. (normal 225 Gm.) with focal fibrosis (healed infarcts); ancient rheumatic myocarditis; (4) coronary sclerosis, grade 2

CASE REPORTS

CASE I. The patient, a man aged forty-five years, gave a history of recurrent attacks of swelling of joints since the age of sixteen years. The last attack had occurred four weeks before an electrocardiogram was taken. There had never been any dyspnea or definite evidences of congestive failure. Blood pressure on admission was 135 mm. of mercury systolic and 85 diastolic. A roentgenogram of the thorax revealed cardiac enlargement with deformity of the cardiac contour. The pulmonary fields were clear. The patient had never received digitalis. The clinical diagnosis was recurrent rheumatic fever with rheumatic heart disease (compensated).

CASE II. The patient, a man aged sixty years, gave a history of anginal pains (exertional) over the past four years. There had been a recent cerebrovascular accident followed by headaches and residua of aphasia and defect of memory. There had been some dyspnea but no actual episodes of congestive failure. Blood pressure on admission was 200 mm. of mercury systolic and 100 diastolic. A roentgenogram of the thorax showed cardiac enlargement but pulmonary fields were clear. The patient was never given digitalis. The clinical diagnosis included coronary and hypertensive heart disease, with angina pectoris, recent cerebrovascular accident and adenomatous goiter without hyperthyroidism.

CASE III. The patient, a man aged forty-three years, gave a history of edema over the past three months, the cause of which was unknown. There had been varying degrees of dyspnea but no pain. No episodes of congestive failure had occurred. Blood pressure on admission was 115 mm. of mercury systolic and 70 diastolic. A roentgenogram of the thorax was negative except for marked cardiac enlargement. The patient had received digitalis for an indefinite period just prior to admission. The clinical diagnosis was possible interauricular septal defect, mitral stenosis (?), and paralysis of left vocal cord (possibly due to pressure from left auricle).

CASE IV. The patient, a woman aged fifty-five years, gave a history of attacks of pain in the right upper quadrant of the abdomen extending to the right shoulder, accompanied by vomiting, fever and headache. She had averaged three such attacks yearly for several years. A non-functioning gallbladder with stones was seen on roentgenographic examination. She had a history of rheumatic fever and seven weeks prior to admission to the clinic she had had a stroke with right hemiplegia from which she had apparently completely recovered. For nine months prior to admission she had complained of nocturnal dyspnea. Signs of congestive failure were in evidence on admission. Blood pressure on admission was 190 mm. of mercury systolic and 90 diastolic. A roentgenogram of the thorax revealed marked cardiac enlargement but pulmonary fields were clear. The patient had taken three capsules of digitalis daily for three months and recently noted some diarrhea and blurring of vision, which raised the suspicion that overdigitalization was the cause of the complete heart block that was present in the first electrocardiographic tracing. This suspicion was strengthened by the fact that bigeminal pulse and premature ventricular contractions were noted on a second tracing taken four hours

after the first. The heart block was absent in a third tracing taken six days later. The clinical diagnosis included hypertensive and coronary heart disease with decompensation and chronic cholecystitis with cholelithiasis.

CASE V. The patient, a man aged sixty-four years, gave a history of questionable mild cerebrovascular accident in July, 1945, with no residua. He was admitted to the clinic on October 2, 1945, complaining of mild exertional dyspnea, but no nocturnal dyspnea. There had been a previous episode of pain in the left anterior portion of the thorax, extending to the left shoulder and arm. There were no definite features of angina pectoris. No previous history of congestive failure could be obtained and there was no evidence of it on admission. Blood pressure on admission was 180 mm. of mercury systolic and 80 diastolic. A roentgenogram of the thorax at the time was entirely negative. This was of interest because a roentgenogram taken at the clinic in 1940 had disclosed a prominent left ventricle. The patient had never received digitalis. The clinical diagnosis was chronic rheumatic aortic and mitral endocarditis with aortic insufficiency.

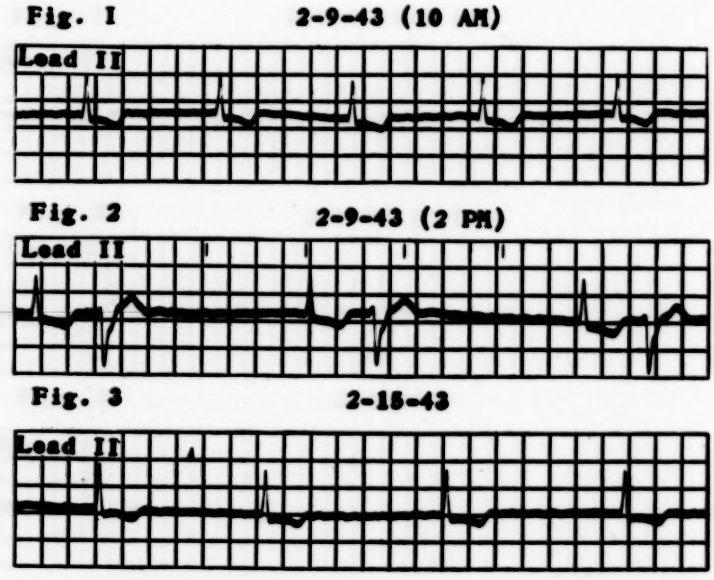
CASE VI. The patient, a man aged seventy-eight years, gave a history of progressive weakness and failing vision. He was admitted to the clinic on July 28, 1944, in a semicomatose state and presented a nursing problem. There had been an episode of congestive failure in 1942 but none since. On admission his blood pressure was 180 mm. of mercury systolic and 90 diastolic. A roentgenogram of the thorax, taken in 1942, had shown marked cardiac enlargement. The patient had taken digitalis in the past, but none recently. The clinical diagnosis was Parkinson's disease with cerebral degenerative changes and arteriosclerosis. Auricular fibrillation with complete heart block first had been noted at the clinic in November, 1934, and was still present at the time of this examination.

CASE VII. The patient, a woman aged seventy-three years, gave a history of episodes of congestive failure since 1934 with dyspnea, edema and so forth, requiring diuretic agents and digitalis. Despite cholecystectomy in 1934 she continued to have attacks of biliary colic, characterized by pain, chills, fever and intermittent jaundice since that time. She was readmitted to the clinic on April 15, 1943, at which time her blood pressure was 124 mm. of mercury systolic and 80 diastolic. A roentgenogram of the thorax had not been taken since 1940 at which time there was marked cardiac enlargement with considerable deformity of the cardiac contour. It is of interest that auricular fibrillation with complete heart block was present in three electrocardiographic tracings taken between April 15, 1943, and April 10, 1944, but that a fourth tracing taken on June 12, 1944, showed that the complete heart block had disappeared. Although she had received digitalis quite regularly since 1934 it cannot be stated with certainty that the drug induced heart block, since typical symptoms of digitalis effect were not in evidence. When the most recent electrocardiogram was taken on September 17, 1945, the heart block was still absent. This strengthens the suspicion that the heart block was a digitalis effect. The clinical diagnosis included chronic rheumatic endocarditis with mitral stenosis and insufficiency and probable common duct stone.

CASE VIII. The patient, a man aged seventy years, gave a history of edema, grade two of ankles with exertional dyspnea and occasional nocturnal dyspnea of several weeks' duration. He had had episodes of congestive failure five years and one year before admission to the clinic. He was admitted to the clinic on May 29, 1945. His condition was easily controlled by administration of digitalis since he had previously been on a maintenance dose of 1½ gr. (0.1 Gm.) daily for five days each week. On May 30, 1945, a transurethral resection was performed for prostatic hypertrophy with obstructive symptoms. This was done with full realization of increased risk of operation. The danger consequent on the degree of urinary obstruction outweighed the cardiac risk, although a roentgenogram of the thorax showed cardiac enlargement with vascular engorgement. The patient died postoperatively from causes unrelated to the heart. The findings at necropsy have been reported earlier in this paper. The clinical diagnosis was arteriosclerotic heart disease with myocardial degeneration and benign prostatic hypertrophy.

CASE IX. The patient, a man aged sixty-five years, gave a history of edema of the ankles, orthopnea, nocturnal dyspnea and sensations of pressure in the thorax, all intermittent, over the two years prior to admission. He had had a probable coronary occlusion in May, 1941, but despite symptoms he was able to work about 50 per cent of the time. There had been several brief attacks of syncope. On admission to the clinic on May 27, 1943, he was found to have ascites, grade 2, and hepatomegaly, grade 2 (on the basis of 1 to 4). A roentgenogram of the thorax showed cardiac enlargement with fluid in the right portion of the thorax. Blood pressure was 210 mm. of mercury systolic and 100 diastolic. The patient had received digitalis intermittently in the past. He was hospitalized for thirteen days, receiving hypertonic solution of glucose, aminophylline and diuretics, but no digitalis. There was a fair therapeutic response. Digitalis was withheld because of the very slow cardiac rate of 31 in the presence of auricular fibrillation with complete heart block. The clinical diagnosis was hypertensive and coronary heart disease with congestive failure. The patient was reported dead on January 14, 1944. Necropsy was not performed.

CASE X. The patient, a woman aged sixty-six years, gave a history of exertional and nocturnal dyspnea, palpitation and attacks of substernal pain relieved by rest over the past two to three years. For some time she had had vomiting at bedtime and before breakfast, together with blurring of vision. These latter symptoms were obviously due to digitalis intoxication, since she had been taking 1 cat unit of digitalis daily for some time prior to admission to the clinic. There had been several episodes of congestive failure. The patient was admitted to the clinic on September 15, 1944, with obvious signs of congestive failure. Our previous electrocardiograms in this case showed that she had had auricular fibrillation without heart block in 1932 and 1935. The electrocardiogram taken on September 15, 1944, revealed auricular fibrillation with complete heart block. The heart block here was undoubtedly a digitalis effect. Roentgenographically there was marked cardiac enlargement. The patient was hospitalized on this admission and the dose of digitalis was reduced to 1 cat unit three times a week. Her symptoms improved. It is probable that the complete heart block disappeared before her dismissal, though unfortunately a second electro-



FIGS. 1, 2 and 3. Only lead II is shown of three serial tracings taken in case IV. Figure 1 represents clearly defined auricular fibrillation and complete heart block. In Figure 2, taken four hours later, note that premature ventricular contractions (bigeminal pulse) are superimposed. Six days later (Fig. 3) all that remains is pure auricular fibrillation. The complete heart block was obviously a digitalis effect.

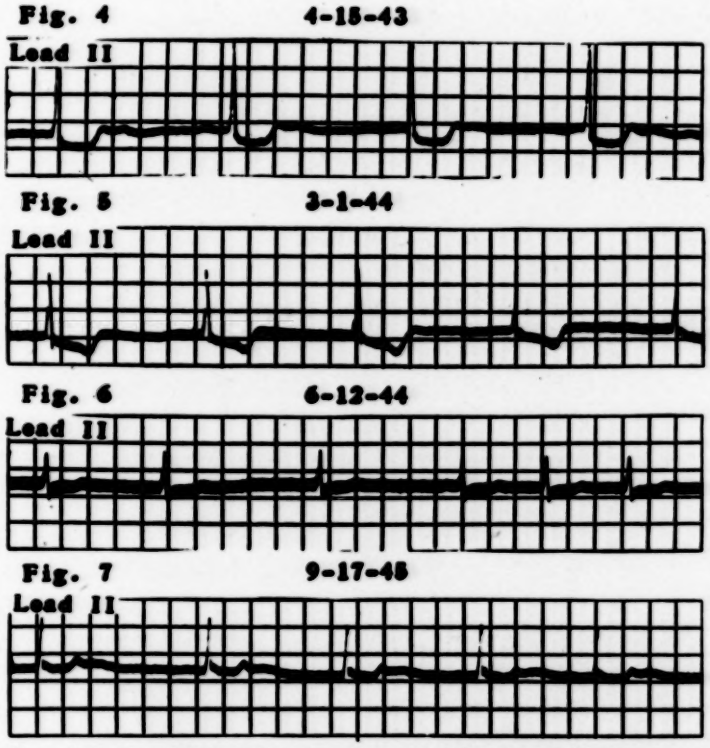
cardiogram was not taken. The clinical diagnosis in this case was arteriosclerotic and hypertensive heart disease.

COMMENT

To establish accurately the diagnosis of concomitant auricular fibrillation and complete auriculoventricular dissociation one must exclude occasional cases of auricular fibrillation in which there is extreme bradycardia in the absence of complete heart block. This can be accomplished by careful measurement of the R-R intervals, which will not be uniformly equidistant in cases of pure auricular fibrillation without heart block. In other words the ventricular rate, though extremely slow, is definitely variable. The criteria used in establishing the diagnosis of auricular fibrillation with complete heart block in this series of cases have been enumerated earlier in this paper.

It has been emphasized that all ten patients had serious cardiac or cardiovascular disease. Therefore, when the heart block is not definitely due to a digitalis effect, its presence with auricular fibrillation implies serious cardiopathy and a poor prognosis. In Barnes's opinion the presence of complete heart block in the absence of auricular fibrillation carries a more favorable prognosis than a combination of the two states, even when the pathologic substrate is the same as the cause of the heart block in either case.

The value of serial electrocardiograms, taken a few days apart, is indisputable in those patients who present themselves with a history of digitalis therapy which has been



FIGS. 4, 5, 6 and 7. Serial tracings in case VII (lead II only). The coved S-T segment in Figure 4 suggests a digitalis effect in itself. However, subsequent changes are more reliable since no coving is apparent in Figures 5, 6 and 7. In Figures 6 and 7 there is pure auricular fibrillation without heart block and this probably was stationary because the same pattern persists in the final tracing. (Fig. 7.) Tracings taken in 1934 showed only auricular fibrillation.

continued for some time, especially when one has not seen these patients previously. If the complete heart block in such cases is due to digitalis, subsequent tracings may show variations in pattern and if the drug is withheld the heart block should finally disappear. This point is well illustrated in Case IV. Figure 1 shows the initial tracing obtained February 9, 1943, when this fifty-five year old woman was admitted to the clinic. Auricular fibrillation and complete heart block are in evidence. In the second tracing (Fig. 2) taken four hours later, premature ventricular contractions (bigeminal pulse) are superimposed, but the heart block is still present. Finally, in a third tracing (Fig. 3) taken six days after the first, there is pure auricular fibrillation without heart block. Since the patient presented only mild symptoms of digitalis intoxication, the dissimilarity of serial electrocardiographic tracings (especially revealing the final disappearance of complete heart block) presented more tangible evidence that we were dealing with a digitalis effect. When the symptoms of digitalis intoxication are slight (as noted in this case) or absent, the presence of complete heart block in addition to auricular fibrillation does not necessarily contraindicate continuing administration of the drug, for in the presence of marked congestive failure further digitalization may be quite rational. However digitalis was withheld in the foregoing case for some time, and there was marked improvement in the patient's congestive failure in response to rest in bed, salyrgan and hypertonic solution of glucose intravenously administered.

Case VII is very similar to Case IV in that the patient presented variable electrocardiographic findings in serial tracings, except that these changes occurred over a period of nearly two years. On April 15, 1943 (Fig. 4) auricular fibrillation with complete heart block was first noted electrocardiographically (previous tracings in 1934 showed only auricular fibrillation). This combination was still present in tracings made on March 1, 1944. (Fig. 5.) However, subsequent electrocardiographic tracings taken on June 12, 1944 (Fig. 6) and on September 17, 1945, (Fig. 7) showed a return to the original pure auricular fibrillation without heart block. In our opinion the complete heart block was a digitalis effect in this case, despite the fact that the patient apparently never had definite symptoms of digitalis intoxication.

It should be mentioned that interference dissociation may simulate complete auriculoventricular block. However, this could easily be ruled out in these cases because in the former condition the ventricular rate exceeds that of the auricles owing to a nodal or idioventricular rhythm. This rare condition is usually attributed to digitalis.[3]

SUMMARY

The interesting phenomenon of concurrent auricular fibrillation and complete heart block has been studied in a series of ten cases. At least two important points are to be gained from this analysis:

1. The presence of this combination, in the absence of digitalis effect, implies a serious prognosis. All ten patients had advanced cardiac or cardiovascular disease.

2. It is important both prognostically and therapeutically to distinguish between complete heart block incident to intrinsic cardiopathy and complete heart block of digitalization. In cases in which symptoms of digitalis intoxication are slight or absent the distinction can be made by observing serial electrocardiographic tracings.

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Electrocardiographic Patterns of Ventricular Aneurysm*

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In several papers the following two electrocardiographic patterns have been described in cases of ventricular aneurysm resulting from myocardial infarction:[1–4] (1) A small r_1 associated with deep $S_{2,3}$; (2) the main ventricular deflection is downward in the three standard leads.

However, not all cases of ventricular aneurysm show these electrocardiographic patterns and these patterns may be present in the absence of an aneurysm. Furthermore the explanation for these patterns has been obscure. We recently studied all cases in which the main ventricular deflections were downward in the standard leads, using unipolar extremity leads as well as standard leads.[5] In this paper we have studied our cases of ventricular aneurysm in the same way.

MATERIAL

A total of forty cases of myocardial infarction were selected for study. These included fifteen cases of ventricular aneurysm diagnosed clinically (by means of both fluoroscopic and x-ray studies of the heart) or at autopsy; one case of rupture of the left ventricle after infarction, confirmed by autopsy; and twenty-four cases of myocardial infarction that showed either of the above patterns, but in whom an aneurysm was absent.

METHOD

Standard leads were taken in the usual way. The unipolar extremity leads were taken using the author's method.[6] The author's indifferent electrode of zero potential was used for the unipolar leads.[2] In addition to these leads, one or more precordial leads were taken. In many of the precordial leads, the left leg was used as the indifferent electrode. In the other cases unipolar precordial leads were taken.[6]

GENERAL RESULTS

Each standard lead represents the difference between the potentials at two extremities. In spite of this fact the following relations usually exist between the standard lead and the unipolar leads that record the potentials at each of the extremities:[7,8,9] Lead I tends to resemble the left arm lead; lead II tends to resemble the reverse of the right arm lead, and lead III tends to resemble the left leg lead.

Cases with the $r_1S_{2,3}$ Pattern. Figures 1B, C, D, E, 2 and 3C, show this pattern. Aneurysms were associated with Figures 1B, C, D and E and were absent in the other cases. When the unipolar extremity leads of these cases are studied, they show the following similar characteristics, regardless of the presence or absence of an aneurysm: (1) Infarction of the anterior wall of the left ventricle was present; (2) the left arm lead tends to show a small r wave; (3) the QRS complex of the right arm lead, which is normally downward tends to be upward, and (4) the left leg lead shows an rS pattern (a small r and a deep S wave). These characteristics can be analyzed in more detail.

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† Work done at Montefiore Hospital, under a Fellowship of the Martha M. Hall Foundation for Research in Cardiovascular Diseases.

Left Arm Lead. When anterior infarction occurs, unipolar leads that overlie or face the epicardial surface of the infarct show a deep wide abnormal Q wave, an elevated RS-T segment and a small or absent final R wave.[8] When anterior infarction is present and the heart lies horizontally, this pattern is transmitted to the left arm lead.[10] Figures 1B and C show this. Wilson has pointed out that the final R wave becomes tall when a unipolar lead faces the margin of the infarct. Figures 1D, E and 2 show a tall R wave in the left arm lead, in spite of the fact that the R is either absent or small in the precordial lead.

In the standard leads, lead I resembles the left arm lead. This produces the small r_1.

Right Arm Lead. In Figures 1C, E and 3C the right arm lead shows a biphasic QRS complex consisting of an initial downward deflection (Q) followed by an upward deflection (R). In Figures 1B, D and 2 the right arm lead shows an initial R wave which may or may not be followed by a downward deflection.

The explanation for the QR pattern in the right arm lead is as follows: A QR pattern is normally found in one or more unipolar leads taken over the upper region of the back, or in esophageal leads above the

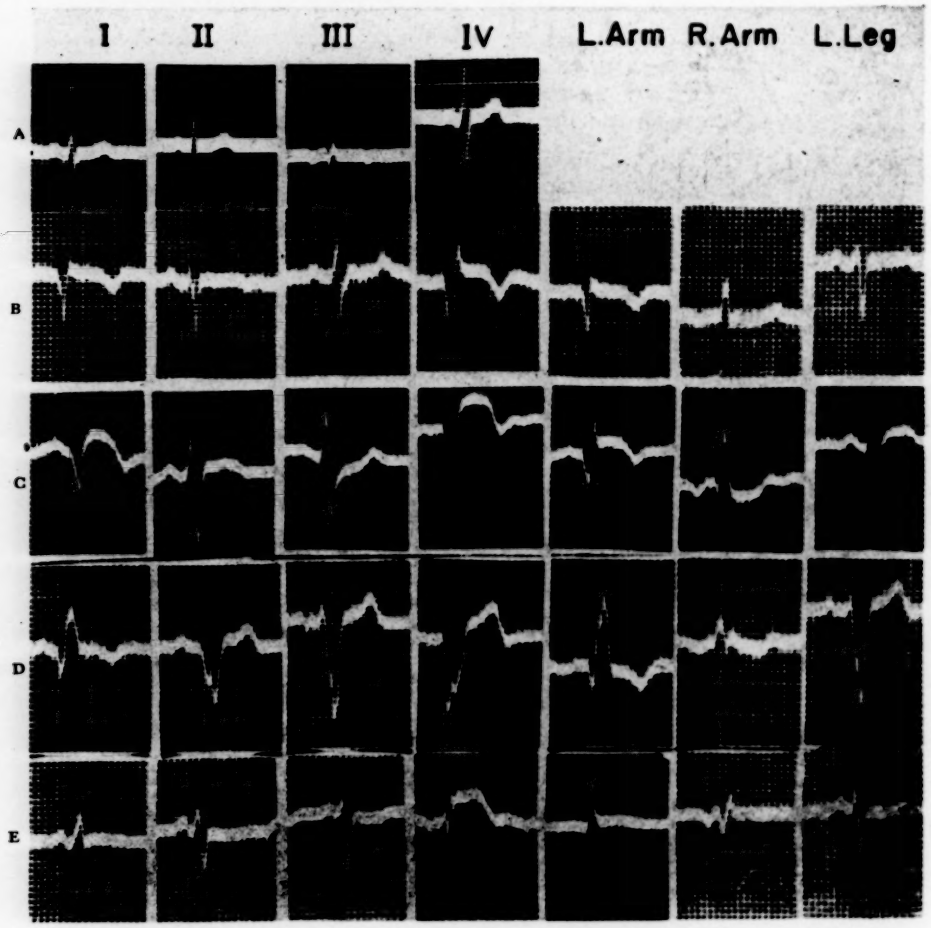

FIG. 1. Cases of ventricular aneurysm that show an $r_1S_{2,3}$ pattern. Left arm, right arm and left leg; augmented unipolar extremity leads. A, B, fifty-nine-year old man. A, taken in 1937; shortly after this he developed an anterior infarct and subsequently a ventricular aneurysm; B, taken in 1944. C, fifty-nine-year old man. D, fifty-six-year old man. E, fifty-eight-year old man. This patient died from rupture of the left ventricle. The tracing was taken the day before he died.

level of the ventricles.[9,10] This pattern can be transmitted to the right arm when marked clockwise rotation of the heart around its long axis occurs.[9,10] The QR pattern in the right arm lead of these cases, therefore, is not a sign of either infarction or aneurysm and merely indicates the position of the heart.

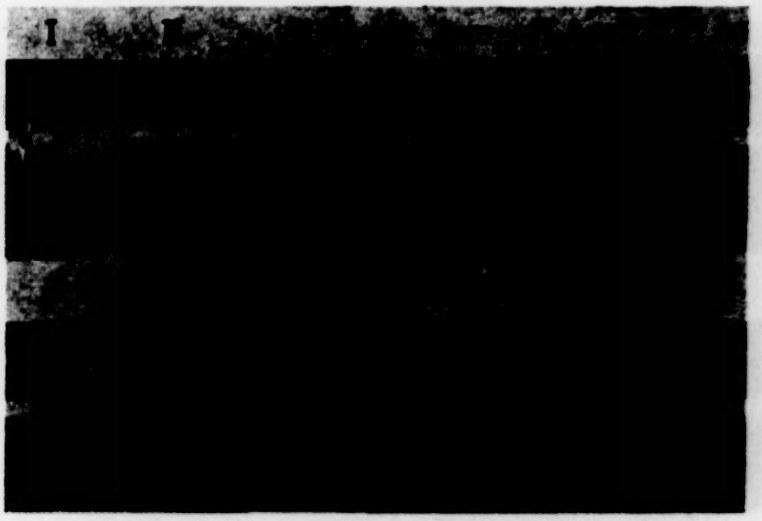

FIG. 2. Tracing that shows the $r_1S_{2,3}$ pattern, without an aneurysm; sixty-two-year old man. V_1 to V_6 are unipolar precordial leads.

The tall initial R wave in the right arm lead is also due to the position of the heart as Figure 2 shows. Notice that in Figure 2 the right arm lead is very similar to precordial lead V_1, which is recorded from the fourth intercostal space just to the right of the sternum. The similarity between these two leads in this case can be explained by assuming that forward rotation of the heart around its transverse axis is present. When this happens, patterns found on the anterior chest wall in the region of the sternum can be transmitted to the right arm lead. Here again, this pattern is neither a sign of aneurysm nor of infarction.

In the standard leads, lead II is often the reverse of the right arm lead. It therefore shows a prominent S wave when the QRS complex of the right arm lead tends to be upward, as in the above examples.

Left Leg Lead. When the heart lies horizontally, the left leg lead faces the epicardial surface of the right ventricle, and shows an rS pattern, even when the heart is normal.[9,10] In the standard leads, lead III resembles the left leg lead. This causes the deep S_3.

Figure 3 shows how the $r_1S_{2,3}$ pattern can occur in a patient with myocardial infarction without an aneurysm This is the tracing of a forty-three year old man who was suffering from an acute anterior infarct. Figure 3A was taken two days after the attack. Figure 3B was taken a week later. Figure 3C was taken two weeks later. The r_1, $S_{2,3}$ pattern is present in Figures 3A and C. It had disappeared in Figure 3B. In other words, the $r_1S_{2,3}$ pattern is a variable one and subject to change. The unipolar extremity leads show the cause of the change because in Figure 3B, in which the pattern is not present, the QRS complex of the right arm lead is downward, whereas in Figure 3C, where the r_1 $S_{2,3}$ pattern has returned, the right arm lead shows a QR pattern.

Cases in Which the Main Ventricular Deflections are Downward in the Standard Leads. Figure 4 shows such a pattern. This patient had anterior and posterior infarctions and an aneurysm of the left ventricle. Figures 1B and C, which show the

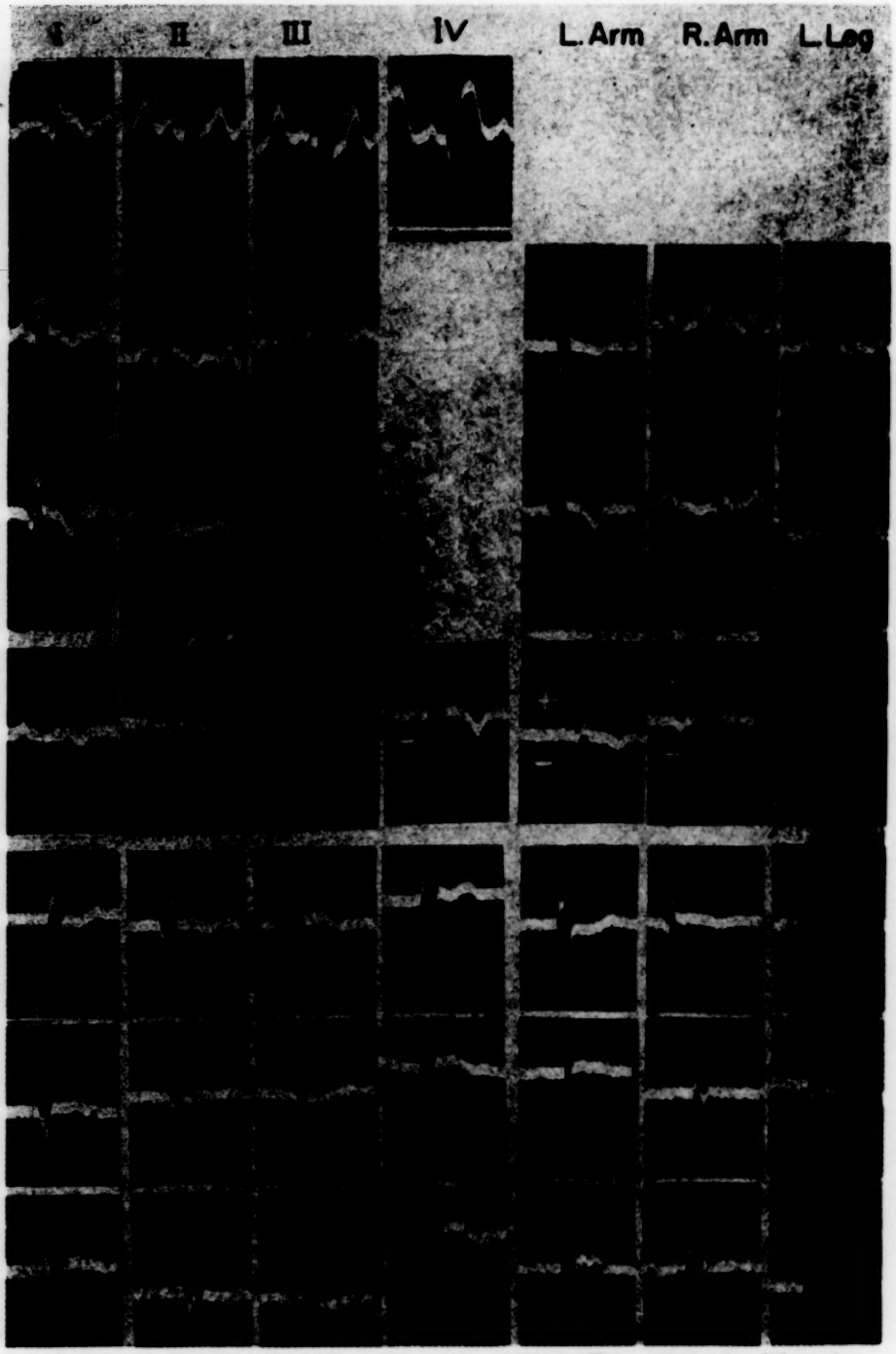

Fig. 3. A patient in whom the $r_1S_{2,3}$ pattern was transient. This patient also did not have an aneurysm. A, taken two days after the patient entered the hospital; B, taken a week later; C, taken two weeks later.

Fig. 4. A case of ventricular aneurysm that shows downward main ventricular deflections in the three standard leads; a fifty-two-year old man.

Fig. 5. Additional cases of ventricular aneurysm. A, fifty-four-year old man; B, fifty-eight-year old man; C, fifty-four-year old man.

$r_1S_{2,3}$ pattern also may be considered in this category. The mechanisms that produce this pattern in the normal and abnormal heart have been reviewed in a previous publication.[5] Here again, in cases of myocardial infarction, the presence of this pattern depends on the location of the infarct and the position of the heart. In all these cases, the unusual position of the heart was indicated by the upward QRS complex in the right arm lead.

OTHER PATTERNS

Figures 5A, B and C show three other examples of myocardial infarction with ventricular aneurysm. In these cases, the tracings do not resemble the patterns just described. However, in these cases also, the upward QRS complex of the right arm lead indicates an unusual position of the heart. Figure 5A is very interesting in this connection. The deep wide Q and coved T in the left leg lead and leads II and III indicate the presence of a posterior infarct. The right arm lead shows a QR pattern. This indicates either marked clockwise rotation of the heart around its long axis or backward rotation of the apex. The elevated RS-T segment in the right arm lead, indicates that the right arm lead is also facing the epicardial surface of the infarct. This further suggests the presence of backward rotation of the apex.

Regardless of the location of the infarct and the patterns in the standard leads, the right arm lead in all our cases of ventricular aneurysm showed an upward QRS complex. This suggests the following: While the upward QRS complex in the right arm lead may occur after infarction, with or without an aneurysm, its absence in the right arm lead, after myocardial infarction, tends to rule out an aneurysm.

CONCLUSIONS

When myocardial infarction occurs the patterns in the standard leads and unipolar extremity leads depend on the location of the infarct and the position of the heart. The presence of a ventricular aneurysm may cause unusual rotation of the heart. When this occurs the standard leads may show an $r_1S_{2,3}$ pattern, or the main ventricular deflections of the three standard leads may point downward. Along with these patterns the QRS complex of the right arm lead tends to be upward instead of downward. However, these patterns may occur in the absence of ventricular aneurysm.

All our cases of ventricular aneurysm showed an upward QRS complex in the right arm lead. This suggests that the absence of this pattern in the right arm lead, in a case of myocardial infarction, indicates that a ventricular aneurysm is absent.

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Review

Cardiovascular Syphilis*

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The last ten or fifteen years have seen a renewal of interest in cardiovascular syphilis, especially in that phase which embraces syphilitic aortitis and its complications. Reëmphasis of the tragic potentialities inherent in the lesion, unless inactivated before symptoms have appeared, has stimulated the setting up of numerous studies designed to establish criteria for the detection of syphilitic aortitis while still asymptomatic and presumably before its progressive course has caused serious damage. By possessing the ability to recognize it in the latent or asymptomatic phase, the physician might then through proper treatment check the relentless progress of the lesion before damage to the aortic wall became serious and in many instances before the process involved the heart or impaired its coronary blood supply.

It cannot be emphasized too frequently that for the medical man syphilis of the cardiovascular system far and away outranks in clinical importance all other late manifestations of syphilis, both because of its serious consequences and its frequency. As to its frequency, syphilis of the aorta and its complications comprises 13 to 15 per cent of all cardiac diseases found at autopsy. To quote Stokes in his opening paragraph on cardiovascular syphilis, it is "ubiquitous, insidious, disastrous."

The exact nature of the pathologic process in the arteries is the subject of some disagreement. Saphir and Scott have contended that the primary lesion is an obliterative endarteritis of the vasa vasorum of the adventitia and that the damage to the media (of serious consequence) is secondary because of impaired blood supply. However, there must frequently be an inflammatory lesion in the media, as miliary gummata and spirochetes have been found in the media itself. Also, the so-called Herxheimer reaction is rather of the nature of a reaction in an inflammatory process in the media itself. Whether the infection is brought from adjacent lymph glands through the lymphatics accompanying the vessels supplying the adventitia, or whether the vasa vasorum bring the infection to the media, is not decided. McMean has suggested that intimal infection may even come by way of the blood stream itself. Inflammatory and healing reactions with the development of fibrosis gradually take place and as the various foci spread they tend, through rupturing the elastic fibres of the media, to produce the flabbiness and dilatation of the vessel such as is seen in a well developed case of aortitis at autopsy. Fibrous thickening of the intima also takes place in plaque formations buttressing the weak spots in the media, thus preventing, in many instances, the occurrence of aneurysm.

In smaller arteries the end result of syphilitic arteritis is often the obliteration of their lumen with the effect of thrombus

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formation. In certain areas this is likely to produce serious results, for example when those arteries supplying the brain and spinal cord are involved. Cerebral softening or complete transverse myelitis may develop suddenly and such lesions may be completely irreversible, especially when terminal arteries without anastomosing branches are attacked. No part of the organism is immune and syphilitic arteritis may be responsible for such diverse conditions as aneurysm of the renal artery finally requiring nephrectomy, or bleeding from a ruptured artery in the gastric mucosa causing death by exsanguination.

Before concentrating the discussion on syphilis of the aorta and its complications, two other manifestations of cardiovascular syphilis deserve brief comment. Unquestionably, syphilitic myocarditis has been found at autopsy but it probably is so rare as to be of no clinical importance, despite Warthin's contention. Any myocardial pathologic changes present in patients with coronary ostial stenosis and incidental associated coronary arterial sclerosis are not syphilitic but merely the result of insufficient blood supply. On the other hand, gummatous involvement of the myocardium, although uncommon, is not so rare but that the clinician who sees much heart disease meets this condition from time to time. The gummatous infiltration occurs most frequently in the region of the septum. Here it interferes with the conduction mechanism, often producing complete heart block. Consequently, with evidence of pathologic changes in the region of the bundle in a patient with positive serologic findings or other signs indicative of syphilitic infection, gummatous infiltration of the myocardium should be given first rank among the various diagnostic possibilities. With nothing suggestive of the presence of syphilitic infection in the patient, consideration of it as a cause of disturbance of the conduction mechanism is almost purely academic.

AORTITIS*

General Considerations. Syphilitic arteritis is potentially most dangerous when it occurs in the aorta. It may weaken the aortic wall and produce an aneurysm. It may involve the aortic ring and extend into the valve itself, producing dilatation of the ring and aortic valvular insufficiency with or without cusp damage and distortion. It may involve the mouths of one or both coronary arteries causing stenosis, atresia or displacement of the coronary ostia.

As to its distribution in the aorta the arteritis may be localized and slight or extensive and severe. It is found most often in the aortic arch, especially in the ascending portion, and not infrequently shows a sharp line of demarcation at the beginning of the thoracic aorta. It is unusual for it to extend below the line of attachment of the aortic valve cusps into the sinuses of Valsalva, despite the fact that in these sinuses the vasa vasorum have a richer distribution. It almost never extends into the myocardium itself below the aortic ring. It may be found only in the thoracic aorta or rarely in the abdominal aorta alone. The anomalous location of the coronary ostia—at or distal to the line of the aortic ring—seems chiefly responsible for their involvement. Von Glahn reported that of the nineteen cases he recorded as showing ostial involvement, only one ostium was in its normal position in the sinus of Valsalva.

Sex, Race and Age Incidence. Syphilitic aortitis is much more frequent in men than in women, who comprise only 7 per cent of our series. As to race, the figures reported

* Unless otherwise specified or evidence is presented as to their reference, figures and percentages used throughout the text are based on the findings in forty-one autopsied patients with primary aortitis occurring on the First Medical Service of Bellevue Hospital between 1929 and 1946.

TABLE I

CASES OF SYMPTOMATIC SYPHILITIC AORTITIS SHOWING DEATHS BY DECADES TABULATED TO SHOW RACIAL DIFFERENCES AND SUBGROUPED PATHOLOGICALLY ON BASIS OF CLINICAL EXPRESSION

Aortitis	A	B*	C	D	E	F	G	H	I	J
	No. of Cases	Per Cent	Death by Decades							Per Cent Dead by Age 50
			20–29	30–39	40–49	50–59	60–69	70–79	80–89	
(All cases)	41	100	1	7	5	15	12	0	1	32
White	29	71	0	3	2	13	10	0	1	18
Negro	12	29	1	4	3	2	2	0	0	67
Subgroups										
Aortic Insufficiency	7	17	0	2	2	2	1	0	0	57
White	3	45	0	1	0	1	1	0	0	33
Negro	4	55	0	1	2	1	0	0	0	75
Aneurysm	9	22	0	0	1	2	6	0	0	11
White	7	77	0	0	0	2	5	0	0	0
Negro	2	23	0	0	1	0	1	0	0	50
Aortic Insufficiency and Coronary Ostial Stenosis	14	34	0	3	0	8	3	0	0	21
White	12	86	0	1	0	8	3	0	0	8
Negro	2	14	0	2	0	0	0	0	0	100
Aortic Insufficiency, Aneurysm	4	9.7	0	1	1	1	1	0	0	50
White	4	0	0	1	1	1	1	0	0	50
Negro	0	0	0	0	0	0	0	0	0	0
Aortic Insufficiency, Aneurysm and Coronary Ostial Stenosis	7	17	1	1	1	2	1	0	1	43
White	3	45	0	0	1	1	0	0	1	33
Negro	4	55	1	1	0	1	1	0	0	50

* In column B, per cent for group is that of entire number; in subgroups, per cent opposite White and Negro is the relative per cent of race in each subgroup.

TABLE II

DECADE OF ONSET OF SYMPTOMS

Cases	20–29	30–39	40–49	50–59	60–69	70–79	80–89	Not Recorded
Total (41 cases)	3	5	6	16	10	0	1	0
White (29 cases)	1	2	3	14	8	0	1	0
Negro (12 cases)	2	3	3	2	2	0	0	0

DURATION OF SYMPTOMS

Cases	Less than 1 Mo.	1 Mo. to 6 Mo.	6 Mo. to 1 Yr.	1 Yr. to 2 Yr.	3 Yr. to 5 Yr.	5 Yr. to 10 Yr.	Over 10 Yr.	Not Recorded
Total (41 cases)	5	7	5	6	9	1	2	6
White (29 cases)	3	5	4	2	8	1	1	5
Negro (12 cases)	2	2	1	4	1	0	1	1

in various articles naturally vary considerably, according to the part of the country in which the reporting hospital is located. In our own series, twelve, or approximately 30 per cent, of forty-one cases are in the Negro race. In respect to age, from the viewpoint of clinical expression, aortitis with its complications is a disease of late middle life. In the Bellevue series the bulk of the forty-one autopsied patients in whom aortitis was primary and not an incidental finding died after their fiftieth year. The two accompanying tables show the percentage of disease found at different decadse, Table I showing the decade in which the patient died and Table II the decade in which symptoms first appeared, as well as length of course after onset. It will be noticed that the disease gives symptomatic expression earlier in life, and its course is definitely shorter in the Negro race than in the white race, also that it causes death in Negroes at a younger age than in whites.

Case histories were not always taken with sufficient care to make the findings as to duration of symptoms valid but they are in harmony with the general impression. The following percentages are based on the total of thirty-five patients in whom complete records were available: 34 per cent were dead within six months; 48 per cent were dead within one year and 66 per cent were dead within two years.

In our total Bellevue series not only did the bulk of the patients, 68 per cent, die after their fiftieth year but 67 per cent did not show symptoms until that age. Even in our patients with aneurysms 45 per cent lived beyond the age of sixty, which was also the period when the greatest number succumbed, while 70 per cent survived to their fiftieth birthday. Of the Negro group, 67 per cent were dead at the age of fifty and 50 per cent of those died from aneurysms.

As previously noted, syphilitic aortitis comprises about 13 to 15 per cent of all cases of cardiac disease found at autopsy. Difference of opinion exists as to whether aortitis is on the increase. It is likely that any increase is only apparent, partly because (as Stokes calls it) our heightened "index of suspicion" has enabled us recently to detect more cases and partly because the increase of the average life span in the last quarter of a century has brought to light patients whose asymptomatic expression had been delayed until the sixth or seventh decade. Only recently we saw a woman in her sixty-ninth year with unquestionable syphilitic aortitis (aneurysmal dilatation and a strongly positive serologic reaction) who for the first time was entering the symptomatic phase with anginal attacks.

Time of Onset with Reference to the Chancre. Because of the late age at which symptoms from syphilitic cardiovascular complications appear, most articles on aortitis have classified it as a late manifestation of syphilis and we know that on the average twenty years elapse after the initial lesion before symptoms occur. As to the actual time of the onset of aortitis after development of the chancre, however, there has accumulated through the years a growing body of evidence which indicates that the inflammatory process in the aorta starts not later than a very few months after the appearance of the chancre. On the validity of this evidence there is fairly general agreement. If we accept Stokes's basic conclusions that "vascular distribution of the infecting agent and injury to the blood vessels form the groundwork of the pathology of syphilis," it is not illogical to suspect that invasion of the blood vessels coincides with the time of the widespread systemic distribution of the spirochetes throughout the body. Certainly, we have evidence that syphilitic aortitis and even its complications may be present many years before they manifest themselves symptomatically. Twenty

years ago Warthin reported the presence of extensive infiltration of spirochetes along the vasa vasorum of the aorta in the few patients with early syphilis that he examined postmortem. His work has not been confirmed by other pathologists. In 1915, Albutt reported on two men who died suddenly in their early twenties, showing syphilitic aortitis with occlusion of one coronary ostium at autopsy. Recently in the draft, three subjects with syphilitic aortic insufficiency were found on induction examination but their ages were not stated. Stokes reports a case with definite signs of aortic involvement six months after a chancre and cites a similar case three months following infection. We have seen a patient with well marked asymptomatic aortic dilatation and valvular insufficiency with strongly positive serologic findings three years after an insignificant penile lesion for which no treatment was sought. Shortly prior to that infection, this patient's heart had been pronounced normal and he had been granted a substantial amount of life insurance.

PATHOLOGY OF AORTITIS AND ITS COMPLICATIONS

Aortitis. The gross appearance of the aorta with advanced syphilitic aortitis is typical—a flabby, stretched tube, irregularly puckered and scarred, with crisscross striations giving it a wrinkled "tree bark" appearance longitudinally. The appearance of the classical lesion is distinctive but when it is overlaid by associated atheromatous changes, as so often happens in the age group in which it is seen at autopsy, the picture of the arteriosclerotic change may completely overshadow that of the syphilitic lesion. Under these circumstances only microscopic examination may reveal its presence. In its progress aortitis often damages the wall of the aorta to the extent that it gradually gives way; it frequently spreads to the aortic valve and damages it to the point that leakage often occurs and it often involves the orifices of the coronary arteries, causing narrowing or even atresia. These various conditions may occur singly or in several combinations, as indicated in Tables I and III.

TABLE III
INCIDENCE OF COMPLICATIONS OF AORTITIS FOUND AT AUTOPSY

Complication	Total Number	Total Per Cent
Coronary ostial stenosis	21	51
Aortic insufficiency	32	78
Aneurysm	20	49

Aortic Valvulitis. When syphilitic aortitis extends into the aortic valve, invasion of the media at the aortic ring causes rupture of its elastic fibres, thereby widening the commissures and increasing the circumference of the ring to a degree that insufficiency of the valve results. In addition, there is often an infiltration of round cells in the aortic cusps which are first thickened and later, as connective tissue retraction occurs, puckered or shrunk so that they fail to meet adequately in diastole, with a resultant increase in the degree of insufficiency.

*Insufficiency of the Aortic Valve.** Pathologic change in the ring is the most frequent cause of valvular insufficiency, for it can produce leakage independently of invasion of the cusps. The combined result of pathologic change in the ring and cusp is an increase in the actual circumference of the ring with a shortening of the edges of the leaflets. As noted from the clinical viewpoint the lesion never extends below the aortic ring into the myocardium or endocardium, nor does it involve the mitral valve.† Today's

* No attempt has been made to follow the criteria of the American Heart Association in differentiating between aortic valve incompetence and aortic valve insufficiency, inasmuch as the lesions in the valve ring producing leakage are on an organic basis.

† Rare instances of both have been reported.

teaching tends to emphasize the incompatibility of the coexistence of aortic insufficiency and stenosis due to syphilitic valvulitis. The argument for this is based on two points; one is that in syphilitic valvular insufficiency the commissures are widened, thus increasing the circumference of the aortic ring, while in aortic stenosis the cusps are fused at the commissures, thus somewhat narrowing the ring. The second point is that calcium rarely infiltrates the ring or cusps in syphilitic aortitis, so that the latter remain flexible and can lie back along the aortic wall in systole even when they are thickened and distorted, with the consequence that no stenosis of the aortic valve is produced. In aortic stenosis, in addition to the encroachment on the lumen by the fusion of the commissures, the valve is further narrowed through the effect that the infiltrating calcium has upon the flexibility of the cusps, particularly at their bases. This causes a stiffening and rigidity which permits little movement in systole and thus narrows the lumen of the valve. In our series of patients with aortic valvulitis with insufficiency, calcific infiltration of the ring and leaflets was present to a much greater degree than we had anticipated, occurring in 7.3 per cent of the patients. We have to revise our thinking in this matter and to accept as a fact that calcific aortic valvular disease as a pathologic entity can overlie a preceding syphilitic valvulitis and produce stiffening and rigidity of the cusps sufficient to cause actual stenosis of the valve, even when the commissures are widened. In all of these patients the commissures were widened and there was adequate histopathologic evidence of syphilitic aortitis. We found damage to the aortic valve with resultant insufficiency in thirty-two of our forty-one patients (78 per cent). In twenty-eight of these, confirmatory clinical evidence of an aortic diastolic murmur was recorded. The aortic valve and the orifices of the coronary arteries are so close together that one would expect both to be invaded in many instances. They showed joint involvement in twenty-one of the patients.

Coronary Ostial Stenosis. Damage to the coronary ostia is of frequent occurrence in aortitis. It has been reported as occurring in 14 to 36 per cent of autopsied patients, but most authors have not differentiated between those patients in whom the syphilitic aortitis was symptomatic and those in whom in its latent form it was an incidental finding at autopsy in a patient dying from some other disease. Our cases of incidental aortitis are too few, only eleven, to draw any statistical conclusions but ostial involvement occurred in 27 per cent. On the other hand, in our primary cases of aortitis it was found in 51 per cent and in 39 per cent of the cases both right and left ostia were conjointly involved. The coronary artery almost never is invaded beyond this area and consequently it is misleading to speak, as Stokes does, of "syphilitic coronary sclerosis." There are only one or two cases of syphilitic endarteritis of the coronary arteries reported in the literature. As a matter of fact, in patients with ostial involvement there is usually less sclerosis of arteries distal to the lesion than might be expected in the corresponding age group. When present, its histopathologic picture is that of arteriosclerosis.

Coronary artery thrombosis is rarely found with coronary ostial stenosis and in fact is a rare complication of syphilitic aortitis,* even when it is overlaid with severe arteriosclerosis. Myocardial infarction* (sine thrombosis) has followed ostial closure but is extremely rare.

* There were two patients with coronary thrombosis and one patient with myocardial infarction (sine thrombosis) in the primary group. In the incidental group, in which syphilitic aortitis was latent, there was a patient with coronary thrombosis, myocardial infarction and multiple points of rupture of the heart wall.

In coronary ostial involvement the heart muscle not infrequently presents evidence of myocardial damage, mostly replacement fibrosis. This is no more than is consistent with the diminished cardiac blood supply produced by the ostial constriction and the degree of associated atheromatous changes present in the wall of the artery itself. In only a few of the Bellevue patients were these striking or sufficient to cause thickening of the artery or narrowing of its lumen. It is certainly impossible to allot the responsibility for cardiac damage directly to myocardial syphilis in the presence of the other two operating forces, especially in the absence of any confirmatory histopathologic evidence.

Aneurysm. The incidence of syphilitic aortic aneurysm can be dismissed in a few words. It is much more prevalent among men than women, as is syphilitic cardiovascular disease in general, and it is found especially among men whose occupations involve severe and sustained strain, such as furniture movers and stevedores. It occurred in 49 per cent of our patients.

Aneurysm of the aorta is the term applied to a bulging area of the arterial wall in which the aortitis has so greatly damaged the elastic and muscular coats that they have lost their integrity and have given way under the strain of the pressure of the circulating blood. The continuous pressure of the wall progressively enlarges the sac (sacculated aneurysm). Eventually, as a rule, the intima is broken and the pressure causes the circulating blood to extravasate into and between the various coats, further disrupting them and hastening the rate of enlargement. The fibrinous debris and stasis at the bottom of the sac favor thrombus formation upon which is laid a laminated clot which increases in size, often to the extent that a large portion of the sac is filled with this material. Simultaneously, however, the blood finds other weak spots in the wall of the sac and tunnels out new areas, so that even though the clot becomes of considerable size and well organized, only rarely through this means is the progressive enlargement of the sac permanently arrested. Sometimes the elastic coat becomes so damaged in the entire circumference of the aorta that by its loss of resiliency a considerable general dilatation of the aorta occurs which may involve a large area or length of the vessel. To this type of aneurysm the name "fusiform" is given. Most aortic aneurysms are in the arch, with the larger percentage in the ascending portion, but they may occur anywhere throughout the length of the aorta. While syphilitic aneurysms may be fusiform or sacculated they are never dissecting. On the other hand, arteriosclerotic aneurysms are characteristically fusiform and only rarely are sacculated. When they assume this form they can be differentiated from those caused by syphilis on occasion only after histologic examination.

CLINICAL ASPECTS OF AORTITIS AND ITS COMPLICATIONS

In considering aortitis clinically, we must constantly remember that syphilitic aortitis is an active, progressive lesion extending over a period of many years. Probably rarely, at its onset, if the invasion is acute, there may be some anginal symptoms, usually vague and fleeting. After that comes a latent period of many years' duration, for *aortitis per se is a symptomless disease.* Symptoms occur only when the damage caused to the openings of the coronary arteries or to the aortic valve is sufficient to impair the cardiac function, or when, from pressure, the wall of the aorta breaks down to the extent that the resulting aneurysm causes damage to other structures in the thorax or to the thoracic cage itself, or on rare occasions dramatically makes its symptomatic stage entrance by rupture.

Here in a nutshell is what makes the prognosis so hopeless in most patients with aortitis once symptoms of cardiac failure occur. The normal blood supply to the heart is obviously diminished and irreversibly so by the narrowing of the coronary orifices. If both ostia are involved, there is little opportunity for the establishment of an adequate collateral circulation through the other avenues of myocardial blood supply. In patients with aortic insufficiency there is obviously a considerable lowering of the diastolic pressure which reduces the volume of blood flow through the coronary arteries, even when the patency of their orifices is unimpaired. This coexists with a gradual increase in the myocardial mass, not infrequently to an enormous degree (cor bovinum), so as finally to be out of all proportion to that which even a normal coronary circulation supported by a continuously adequate pressure of blood is adapted.

CORONARY OSTIAL STENOSIS

Symptoms. The presenting symptoms are usually those of slight impairment of the coronary circulation, either angina or dyspnea. We have found dyspnea more frequently, although most reports favor angina. Dyspnea, when paroxysmal, is often nocturnal, commonly awakening the patient from sleep. The intensity of this symptom increases rapidly and it is soon followed by frank failure of the left and right heart in rapid succession.

In ostial stenosis, attacks of angina may be of such frequency and severity as to incapacitate the patient and may persist despite complete bed rest. A syndrome of acute coronary failure occasionally seen in syphilitic aortitis with ostial stenosis is that of sudden fulminating pulmonary edema. One woman who was an inpatient on the First Medical Service of Bellevue Hospital continuously for over two years, not only had anginal pain so severe as to require repeated nerve block but also had many attacks of sudden and alarming pulmonary edema, to one of which she finally succumbed. Postmortem examination showed aortitis with fusiform aneurysmal dilatation, stenosis of both coronary ostia and aortic valvular insufficiency.

Physical Signs. Coronary ostial stenosis even in its symptomatic stage gives no physical signs. In patients believed to have syphilitic aortitis without aortic valvular insufficiency or hypertension, we may ascribe to coronary ostial stenosis any attacks of paroxysmal dyspnea or angina. Under the same restrictions we may consider it responsible for cardiac failure if the heart shows little or no enlargement and if the signs are suggestive of dilatation rather than hypertrophy. As attacks of angina may have preceded the heart failure, coronary thrombosis with myocardial infarction must be ruled out. In none of our patients was coronary ostial stenosis the only complication of syphilitic aortitis, and consequently the physical signs were simply those of the associated lesions. If in syphilitic aortitis ostial narrowing were present alone and had progressed to the degree of causing symptoms of impairment of the coronary circulation or of heart failure, there would be no physical signs by which it could be distinguished. The only physical signs would be those of the underlying aortitis such as the following: If emphysema is not present, some supracardiac dullness at times may be elicited if moderate dilatation of the arch has occurred. Even without aneurysm, a slight sense of pulsation at times can be felt just at or above the aortic area at the right sternal margin.* The aortic second sound is accentuated and without hypertension it is low pitched. Frequently

* This frequently may be appreciated better by placing the ear over the pulsating area than by the usual manual methods.

it is said to have a typical "tambour" quality but, as a rule, it is not sufficiently characteristic to enable one to detect its peculiar quality, except under especially favorable conditions. Certainly, with coexistent hypertension, as so often happens in syphilitic aortitis, the quality of the aortic second sound is not characteristic. However, in the absence of hypertension or of a mediastinal shift to the right, accentuation of the aortic second sound, especially if its pitch is low, should arouse suspicion of syphilitic aortitis, irrespective of whether the specific tambour quality is recognized.

If the change in lumen is sufficiently abrupt in dilatation of the ascending portion of the aortic arch, a systolic murmur, usually soft, may be present in the right second interspace near the sternum. This murmur is rarely heard over the right carotid artery, as are the harsher murmurs of both aneurysm and aortic stenosis. Fluoroscopic examination may give confirmatory evidence of aortic widening or may show increased amplitude of pulsations in the ascending portion of the arch.

AORTIC INSUFFICIENCY

Symptoms. The initial symptoms, as in coronary ostial stenosis, are those of impairment of the coronary circulation or are suggestive of cardiac embarrassment. Both paroxysmal nocturnal dyspnea and angina can be frequent and severe and as the symptomatic stage progresses symptoms and signs of cardiac failure appear. While at first limited to the left side of the heart, signs of right-sided failure rapidly supervene.

Physical Signs. The physical signs peculiar to the lesions are as follows: The most important sign, without which one may suspect but cannot diagnose aortic insufficiency, is a blowing diastolic murmur. This murmur varies in intensity from a softness too faint to be heard except with the direct ear or diaphragm type of stethoscope and then possibly only on full expiration in the upright position, to a harsh, readily audible blow. Its point of maximum intensity is usually in the left third or fourth interspace near the sternal border but it may be heard to the right of the sternum and is more often heard in this area in syphilitic valvular involvement than in aortic insufficiency from other causes. The pitch is usually high. Rarely, the murmur may be heard only near the apex. It may be readily differentiated from the murmur of mitral stenosis by its high pitch and blowing quality, while the latter is a low pitched rumble. With insufficiency of the aortic valve present the dilatation of the aortic arch is likely to be greater and the systolic murmur louder and harsher. The aortic second sound usually remains accentuated but in patients with decided increase in the circumference of the ring and distortion of the valves it diminishes in intensity or becomes inaudible. The pulse assumes a characteristic rapid rise and fall (Corrigan pulse), a "pistol shot" sound is audible in auscultation over the femoral arteries and visible pulsations of the carotid arteries sufficiently great to lift the earlobes in systole are present. A blowing systolic murmur of relative mitral insufficiency is usually present and not infrequently an Austin Flint murmur also. This murmur is heard in late diastole and is located just within the apex. It is of a rumbling or, more rarely, a wavy quality and cannot be differentiated by the quality of its sound from the many variations which occur in the diastolic murmur of mitral stenosis. Its presence was noted in 46 per cent of our patients with aortic insufficiency in whom murmurs were recorded. The heart is enlarged to the left, sometimes to an enormous degree, the apex being thrust downward and laterally from its normal position to the sixth or seventh space. Even in patients with extreme enlargement the

apical impulse is usually fairly well localized, although with much dilatation it may be feeble and ill defined. There also may be some enlargement detected as dullness on percussion to the right of the sternal border. However, dullness is not present over the conus area, nor is a diastolic shock palpable in the left second or third space near the sternum. As bundle branch block rarely exists in syphilitic aortic insufficiency, the pulmonic second sound is practically never accentuated as it is in mitral stenosis. This contrast helps in the differential diagnosis. Extreme cyanosis is rare, even with decided hepatic enlargement, in contrast with the degree commonly found in mitral stenosis and cor pulmonale. Engorgement of the liver is likely to be very painful, probably because its rapid development suddenly distends the capsule. It is often of such intensity that the organ feels too firm for simple passive congestion. Auricular fibrillation occurs only occasionally, in contrast to its frequent occurrence in the hypertensive heart and mitral stenosis. In the latter, if of long standing, regular sinus rhythm is so rare that its presence is suggestive of a complicating subacute bacterial endocarditis.

ANEURYSM

Any discussion of the clinical aspects of aneurysm of the aorta, in as condensed a presentation as this, is immediately hampered by the fact that symptoms and physical signs vary so extraordinarily. Even in aneurysm limited to the arch of the aorta, they depend not only upon which portion of the arch is involved but also upon the direction in which the aneurysm extends and the extent to which it exerts its disastrous compressing effects upon the various structures in the thorax and the bony cage. Therefore, it would seem wise to make no attempt to describe in detail the symptoms and findings at various sites throughout the aorta, together with their several directions of extension but to emphasize chiefly those "key" findings which should arouse the physician's suspicion of the presence of this serious complication.

Just as aortitis exists without symptoms or signs, aneurysm also may be present in silent form; even when symptomatic, one may be unable to elicit any physical signs and comparison of postmortem with clinical diagnoses emphasizes the large proportion of aneurysms that are first recognized at the postmortem table.

Symptoms of Aneurysm of Aortic Arch. In aneurysms of the ascending portion of the arch the early symptoms may be similar to those of aortitis with coronary ostial narrowing but they differ slightly in detail.

Pain is a frequent complaint but, unlike angina, is usually more steady and pressing and occasionally influenced by posture. When the vertebrae are pressed on or eroded, pain may be felt in the back or radiating around the ribs "girdle" fashion. With this there may be at times a "stitch" on inspiration, leading to an erroneous suspicion of pleurisy. Dyspnea when it appears, unless caused by an associated ostial stenosis, is constant. It may have exacerbations, not infrequently nocturnal, but as these are caused by transient episodes of either bronchospasm or edema of the bronchial mucosa, these paroxysms take on a wheezing or asthmatic character. An additional symptom often is cough which is dry, harassing and aggravated by effort. If narrowing of the bronchus through pressure is sufficient to cause "puddling" of secretion distal to the constriction, it may become productive. Blood-streaked sputum usually indicates erosión of the bronchial mucosa, although infrequently it is a forerunner of a sudden, large, exsanguinating hemorrhage caused by rupture of the aneurysmal sac into the bronchus. When

an aneurysm of the transverse portion of the arch of the aorta produces paralysis of the left recurrent laryngeal nerve, the patient's cough assumes a peculiar "brassy" quality which is pathognomonic. By simply hearing it on entering a ward, the experienced clinician can make an accurate "snap" diagnosis of aneurysm of the transverse portion of the aortic arch. The combination of pain, dyspnea and cough should always arouse suspicion of aneurysm of the arch of the aorta. When aneurysm is present and unrecognized, routine arsenical therapy given because of other indications of syphilis is likely to cause these symptoms to be suddenly aggravated after each intravenous arsphenamine injection.

Physical Findings of Aneurysm of Aortic Arch. The most constant and important abnormality is a greatly accentuated aortic second sound. Its significance is much increased when, in addition, a sense of shock can be felt in diastole in the right second space near the sternum. One should mention that this is a sign which may be missed easily if not looked for. If, in addition, the left brachial pulse (radials are more likely to be aberrant) is smaller than the right, aneurysm of the ascending or transverse portion of the arch is almost sure to exist. With this the systolic blood pressure in the left brachial is relatively lower than compatible with its normal variation (normal average difference 10 mm. of Hg), and in cases where the difference in size between the two pulses is too slight to be detected this difference in systolic pressure is in itself diagnostically significant.

In aneurysm of the ascending portion of the arch a systolic thrill of variable intensity may be felt over the base. As in aortic stenosis it may be palpable at times only with the patient in the prone position with the breath held in forced expiration. Accompanying this thrill there is usually a harsh systolic murmur over the right carotid.

A diagnostic aid in aneurysm of the transverse arch is "tracheal tug." This is a downward pull of the trachea in systole felt by upward pressure on the lower border of the larynx by the thumb and index finger. It is not to be confused with the pulsations of the thyroid arteries, extending laterally in this region, which frequently are misleading. Examination of the larynx may reveal a partial or complete paralysis of the left vocal cord. Any or all of these signs may be present on physical examination with no other abnormal findings in the chest. On the other hand, there may be decided widening of the manubrial dullness. Pulsation about these areas of dullness more frequently can be seen as a general heave in the area involved than actually felt. Rarely, a presenting rounded bulge with true expansile pulsation is present. This occurs when the aneurysmal sac projecting forward has eroded the sternum and escaped from within the thoracic cavity. The trachea at times is displaced. Suppressed or wheezing breath sounds are heard over one lobe of a lung, usually the left upper lobe, if the aneurysm has compressed and narrowed a large bronchus. Puddling of secretions behind the area of compression may cause inflammatory reaction, pulmonary consolidation and also bronchiectasis.

Roentgenologic Findings of Aneurysm of Aortic Arch. If the aneurysm is relatively small and pointed posteriorly the routine postero-anterior film may show no suggestion of it, as its shadow may be revealed only by a film taken in the left anterior oblique or more rarely in the lateral position. Usually, however, a postero-anterior film reveals a decided extension in the shadow of the arch of the aorta. The shape and position of this shadow, especially if continuous with the silhouette of the aorta, together with the clinical findings, will usually warrant a

diagnosis of aneurysm, especially if the shadow shows a well marked pulsation on fluoroscopy. Occasionally, one can see no pulsation on fluoroscopy, either because of a laminated clot or a mediastinitis.

Aneurysms of the Thoracic and Abdominal Aorta. These deserve a few comments. In the former, pain in the back from pressure on the spine is frequent. Examination may reveal dullness or a sense of pulsation to the left of the spine below the interscapular region. Occasionally an expansile pulsating mass may be present. They frequently rupture into the left pleural cavity. X-ray films may show partial destruction of the lower thoracic vertebrae.

With regard to aneurysms of the abdominal aorta, in the past authorities have stated that they were rarely syphilitic in origin even when sacculated and that they did not occur independently of aneurysmal involvement of the aorta above the diaphragm. Both of these statements have been proved erroneous.

In recent reviews of the literature which have excluded cases reported in the pre-Wassermann era and those in which with a negative serologic reaction the diagnosis (either syphilis or arteriosclerosis) was not supported by histologic evidence, analysis of accepted cases has shown that of all aneurysms of the abdominal aorta 58 per cent are syphilitic in origin and of those located in the upper portion of the vessel 75 per cent are syphilitic in origin. Furthermore, they have been found to exist independently of syphilitic aneurysms of the aorta above the diaphragm.

Those that are syphilitic in origin are more likely to produce symptoms than those on an arteriosclerotic basis. Pain is the most frequent symptom. It is steady, boring, usually in the back and is worse at night. It may be girdle-like and influenced by position. Vague digestive disturbances may be present. Occasionally the patient is aware of a mass or is shaken by a sense of pulsation.

Examination reveals a pulsating mass. Often it is difficult to determine its expansile quality, or to decide whether pulsation is in the mass itself or whether it is merely transmitted from a normal aorta adjacent to it. If the mass is an aneurysm a bruit can often be heard over it. In many cases a systolic thrill may be felt.

Confirmatory signs may be a difference in size between the femoral pulses if the aneurysm is in the lower abdomen or if one iliac artery is partially blocked by thrombus formation. Blockage of distal arteries by embolus may occur.

Rarely, roentgen films show a wide aortic shadow but often reveal erosion of the anterior portion of the vertebral bodies. Death is often caused by rupture into the peritoneal cavity.

DIAGNOSIS OF AORTITIS AND ITS COMPLICATIONS

Any discussion of the diagnosis of syphilitic aortitis separates itself naturally under two headings: (1) The clinical recognition of the complications of aortitis and their differentiation from various lesions presenting points of similarity clinically. The problems involved are encountered almost wholly after the patient's aortitis in its progress has reached the symptomatic phase. (2) The attempt to recognize the presence of syphilitic aortitis when encountered in the asymptomatic phase and, if possible, before any of its serious complications—coronary ostial stenosis, aortic valvular insufficiency or aneurysm—have occurred.

Before entering into detailed discussion of either of the headings just listed it may not be amiss to warn the practitioner that on the basis of evidence furnished by comparison of clinical diagnoses with the corresponding postmortem findings, the

recognition of syphilitic aortitis, even in its symptomatic stage, appears to be fraught with considerable difficulty. The chief causes of our confusion are: (1) the time of life at which the complications of syphilitic aortitis have progressed to the symptomatic stage is also the period when these same pathologic conditions (aortic aneurysm, aortic valvulitis and coronary artery disease) but with different etiologic bases, enter upon the stage of their clinical expression; (2) irrespective of whether syphilis, arteriosclerosis, etc., is the underlying etiologic factor, there are more points of similarity than difference in their clinical expression; and (3) by the time the symptomatic stage of syphilitic aortitis has been reached, the lesion is often overlaid with extensive arteriosclerotic changes and may be obscured by the pathologic changes and clinical findings of a concomitant hypertension or calcific aortic valvulitis.* The manifestations of arteriosclerosis and hypertension dominate the clinical picture so commonly later in life that when they are associated with syphilitic aortitis, this lesion is so masked that the unalert physician does not even suspect its existence until autopsy reveals its presence. Nevertheless, although frequently masked, there are clues through which syphilitic aortitis in its symptomatic phase may be uncovered. However, these are not in the nature of clearly painted sign posts for the direction of the indifferent medical traveler. For the physician to recognize that one of the complications of syphilitic aortitis is the fundamental lesion in the clinical picture, it is of paramount importance that he be acutely aware that syphilis may be at the back of every cardiovascular disorder under his care. Then, and then only, will he make a serologic test a routine part of his examination of a patient, be alert to checking fine points of clinical differentiation and finally, seek that corroborative evidence of syphilitic infection which is essential in obscure cases when serologic evidence is lacking.

In weighing evidence the following points may be helpful, especially when cumulative: (1) In cardiovascular disease, as between men and women, syphilis is likely to be an etiologic factor in the proportion of 5:1. Thirty-eight of our forty-one patients were men, a ratio of 13:1. (2) While it rarely produces symptoms before the age of thirty-five, from then on aortitis may be expected to show itself with progressively increasing frequency through the fourth and fifth decades. Age beyond that time is no bar to its occurrence, as attested by one of our autopsied patients who presented symptoms at the age of eighty. (3) Cases of cardiovascular disease in the third and fourth decades, especially those in which cardiac failure exhibits rapid progress, are much more likely to be syphilitic when found in the Negro race. (4) Admission by the patient of the existence of a previous penile sore weighs the scale heavily in favor of syphilis. (5) A positive serologic reaction, especially in the later decades, makes it unlikely that other factors, such as arteriosclerosis or rheumatic fever, are the basic causes of any cardiac clinical picture under consideration.

In cardiovascular syphilis one often fails to obtain a positive serologic reaction. Twenty-five years ago it was positive in only about 60 per cent of the cases reported. More recently this average has risen to 75 per cent, and today one may expect that the greater sensitivity of the tests will show an even larger percentage of positive reactions. In our series the Wassermann test gave a strongly positive reaction, either in blood or spinal fluid, in 85 per cent of our patients in whom the test was recorded

* Rheumatic aortic valvulitis also may obscure the diagnosis, even in the later decades and all pathologists have not accepted calcific aortic valvular disease as an independent pathologic entity.

and a weaker one in 2.4 per cent more.* With a negative reaction to the Wassermann test the employment of the Kline and Kahn tests should be routine because of their greater sensitivity. While less specific, a positive reaction may be accepted as confirmatory evidence of syphilis when obtained in conjunction with a clinical syndrome suspected of being on a syphilitic basis. Failure to obtain a history of a chancre is common. In some series it has been as high as 50 per cent. Adroit questioning may elicit admission of a previous venereal infection and the percentage of patients with neither a positive serologic reaction nor a history of venereal disease is probably not more than 10 per cent. In these patients particularly, corroborative evidence of the presence of syphilis which careful search may reveal is most necessary. This evidence may include signs of previous periostitis, a penile scar, suggestive dermal scars or a small patch of active syphilid. A search should always be made for a perforated nasal septum which is of great significance in the absence of any previous nasal operation.

As approximately one-third of the patients with syphilitic aortitis present signs of early syphilitic involvement of the nervous system, additional evidence on which to base a presumption of a syphilitic element in the cardiovascular picture may be secured through a neurologic examination. The general practitioner should train himself in the routine and technics of a neurologic examination so that he may elicit the abnormal neurologic signs. Among these may be mentioned irregularity, inequality, decided contraction, fixity or sluggish reaction of the pupils. Argyll-Robertson pupil and oculomotor palsies of recent origin are of significance. Changes in the deep reflexes may be obtained, and if early tabes is present, Achilles tendon and testicular sensitivity may be diminished. If a spinal test is not contraindicated, the spinal fluid may reveal supporting evidence of syphilis, ranging from a slight increase in cells or protein to characteristic changes in the gold curve or strongly positive serologic findings. These may occur with a negative serologic reaction.

* In four of the seven patients in whom no serologic test was recorded, the patient died the day following admission; one other died four days after admission.

DIAGNOSIS OF SYPHILITIC AORTITIS IN ITS SYMPTOMATIC STAGE

In clinical syndromes indicative of aortic aneurysm, aortic valvulitis or impairment of the coronary circulation, we have just discussed those factors and data constituting the indirect evidence in favor of syphilis as the etiologic factor. In addition, there are in the specific syndromes a few points of clinical differentiation of sufficient importance to warrant discussion in detail.

*Narrowing of the Coronary Ostia.** The conditions with which this may be confused are angina pectoris (on the basis of coronary sclerosis); myocardial infarction after coronary thrombosis; early cardiac failure on the basis of hypertension and coronary sclerosis; and pulmonary edema in acute dilatation of the left heart from other causes. As hypertension and enlarged heart are frequently associated conditions, no clean-cut differences are obvious. However, in ostial stenosis, angina is usually more severe and progressive and because of ostial obstruction rather than arterial spasm, it is not so likely to be influenced favorably by nitroglycerin. Occasionally the duration of an anginal attack is so long that it suggests myocardial infarction but there is no temperature, leukocytosis, increased

* As coronary ostial stenosis did not occur in our series independently of either aneurysm or aortic valvular insufficiency, despite its frequency except in the asymptomatic group, this discussion is simply for the purpose of emphasizing the symptoms of impairment of the coronary circulation.

sedimentation rate or characteristic electrocardiographic changes such as one finds in the latter. If the heart is but little enlarged, the blood pressure normal and there is a slight dilatation of the aorta and the aortic second sound accentuated and low pitched, attacks of angina or pulmonary edema are much more likely to be on the basis of syphilitic narrowing of the coronary orifice. In general, the electrocardiograph gives no characteristic changes; there may be some splintering of the ventricular complexes, indicating some myocardial damage, and depressed T waves or a depressed ST segment. Even the electrocardiographic changes in response to the anoxemia test simply indicate impairment of the coronary circulation without regard to underlying pathologic changes.

Insufficiency of the Aortic Valve. When this lesion complicates syphilitic aortitis we have to distinguish it from the following conditions: rheumatic aortic insufficiency with or without stenosis, calcific aortic valvular disease, aortic insufficiency on an arteriosclerotic basis, aortic incompetency in hypertension and, more recently, healed bacterial endocarditis with aortic valvular leakage and progressive cardiac failure.

In the first, there may be a history of rheumatic fever. If not seen in the first bout of heart failure, there may be a history of heart distress and even attacks of repeated failure extending over a period of time much longer than usually compatible with life after failure occurs in the syphilitic heart. Furthermore, compensation may be satisfactorily restored in the intervals between breaks, and cardiac failure may recur only because of some respiratory infection, recurrent rheumatic activity* or because the patient has stopped digitalis. While a mitral diastolic murmur may be present in both conditions, the other signs suggestive of mitral stenosis usually are present in the rheumatic case, namely, an accentuated pulmonic second sound with a diastolic shock, increased dullness over the conus area, and the characteristic x-ray silhouette. This last will be lacking in the syphilitic heart, as will the esophageal displacement by an enlarged left auricle. Auricular fibrillation, rare in syphilitic heart disease, is common in rheumatic heart disease.

In calcific aortic disease the pulse is usually smaller and rarely Corrigan in type. It rises slowly in systole and may have an anacrotic notch. Often the diastolic murmur is inaudible and, when heard, is usually faint. The second aortic sound is either much diminished in intensity or absent over the area of the right carotid artery. A systolic thrill is usually palpable over the right second interspace near the sternum. It is most readily felt with the patient lying prone and holding his breath in forced expiration. In sacculated aneurysm of the ascending portion of the arch, a thrill may also be present, and the pulse may have an anacrotic notch; but in this condition the aortic sound will be accentuated and probably accompanied by a diastolic shock. When syphilitic aortic insufficiency and calcific aortic disease coexist, a high degree of diagnostic acumen may be necessary to recognize the presence of the syphilitic disease.

If aortic valvular insufficiency is associated with the aneurysm, the aortic second sound may be absent, as in calcific disease if the associated valvular damage is sufficiently great. Usually, evidence of much greater aortic dilatation is present than is found in calcific disease. The diastolic murmur is loud, in contrast to the faint murmur described above, and the pulse is large and suggestively Corrigan in type, despite its atypical systolic phase. When, even without aneurysm, the dilatation of

* In active rheumatic carditis, the erythrocyte sedimentation rate is usually elevated even in the presence of chronic passive congestion.

the vessel in syphilitic aortitis produces a murmur sufficiently rough to resemble that of aortic stenosis, then with aortic valvular insufficiency present, the diastolic murmur is usually correspondingly loud. Furthermore, it is frequently loud to the right of the sternum, which is unusual in other conditions; also, the aortic second sound may be accentuated.

Clinically, incompetence of the aortic valve may be caused by the stretching of the ring by excessively high blood pressure. This could be confused only with slight grades of aortic valvular insufficiency due to syphilis. It is found rarely except when the systolic pressure is above 250. It is usually transitory, disappearing when the blood pressure drops below this point. The pulse is usually not Corrigan in type.

There are other cases which, although they form a small percentage of the total, make an appreciable group combining dilatation of the aorta and aortic valvular insufficiency. Whether or not they all fall into the same category, and whether fundamentally they all have the same pathologic changes is an open question. In all probability, some of them are on an arteriosclerotic basis and some are combined syphilis and arteriosclerosis. Clinically, they present a well marked aortic valvular insufficiency without other valve involvement, and often have considerable fusiform dilatation of the aortic arch. One such group has been described in the last two years, in which there is dilatation of the aortic ring and lesions of the cusps, with histopathologic changes differing from those found in syphilis, and without associated syphilitic aortitis. Clinically, they are extremely difficult to differentiate from those cases of syphilitic aortitis with negative serologic reactions and no venereal history.

Acute bacterial endocarditis, hitherto a fatal disease, is cured now by the use of penicillin. In aortic valvular involvement, if much damage has occurred, a definite valvular insufficiency takes place. This is on the basis of ulceration of a valve leaflet by the bacterial lesion and leads to clinical manifestations of aortic valvular insufficiency, with a diastolic murmur and Corrigan type of pulse, when considerable damage to the leaflet has occurred. Symptoms of circulatory embarrassment are rapidly progressive, leading to cardiac failure with fatal outcome. Without the history it is practically impossible to distinguish between this and syphilitic aortic insufficiency on examination. However, in patients with valvular damage due to preceding bacterial endocarditis, the diastolic murmur is usually much rougher and lower pitched than one would expect to find in syphilitic aortic insufficiency; and it frequently has the musical quality usually associated with a ruptured cusp. Also, there may be a diastolic thrill, a most unusual finding in syphilitic aortitis. There may or may not be a systolic murmur, because without arteriosclerosis there is little aortic dilatation.

Aneurysm. Occasionally, the shape and location of an aneurysm may be compatible with that of a mediastinal mass such as tumor, Hodgkins' disease or substernal thyroid. (If, on account of suspicion of syphilis, treatment is instituted, Stokes states that pulsation along the border of the shadow may finally appear after the periaortitis is dissipated.) Erosion of the vertebrae from an aneurysm may lead to an erroneous diagnosis of Pott's disease, or a lower thoracic or upper abdominal aneurysm may give symptoms suggestive of abdominal visceral changes. In the absence of radiographic evidence of visceral disease, syphilis, especially neurosyphilis or aneurysm, should always be considered in seeking evidence of some cause operating to produce the patient's symptoms.

A sudden hemorrhage from the mouth, sufficiently large to exsanguinate, almost al-

TABLE IV*

CLINICAL AND PATHOLOGIC DATA OF BELLEVUE SERIES

CASE NUMBER	SYPHILIS PRIMARY	SYPHILIS INCIDENTAL	SEX	RACE	AGE	DAYS IN HOSPITAL	PATHOLOGY: AORTITIS: Arch	AORTITIS: Thoracic	AORTITIS: Abdominal	AORTITIS: Uncomplicated	AORTITIS: With Sclerosis	ANEURYSM: Ascending	ANEURYSM: Transverse	ANEURYSM: Descending Thoracic	ANEURYSM: Abdominal	HEART: Dilated	HEART: Hypertrophied	HEART: Weight (in grams)	AORTIC VALVE: Valvulitis	AORTIC VALVE: Widening of Commissures	AORTIC VALVE: Invasion of Cusps	AORTIC VALVE: Insufficiency	AORTIC VALVE: Sclerosis of Valve	CORON. OSTEAL STENOSIS: Right	CORON. OSTEAL STENOSIS: Left	CORON. OSTEAL STENOSIS: Both	ARTERIES LUMEN: Narrowed	ARTERIES LUMEN: Patent	ARTERIES LUMEN: Sclerosed	ARTERIES LUMEN: Thrombosed	ASSOC. PATHOLOGY: Pneumonia	ASSOC. PATHOLOGY: Tuberculosis	ASSOC. PATHOLOGY: Erosion	BLOOD PRESSURE
1	+		M	W	67	+	Sl.				4+						+	800	+	+			+	+	+	0	0		+						150/80
2	+		M	W	59	10	4+					Top +					Sl.	NR	+	+			+		0	0	0		+						NR
3	+		M	W	65	+	+				+						+	550	+	+	+	+	+		+	+	+	+	+	+	+				140/50
4	+		M	W	80	5	Dil. +				+	+				+	+	NR		+			+		+	+	+	+	0	+	+				150/50
5	+		M	W	67	+	+	+	+					2	+	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR			+	R 150/98 L 118/98
6	+		M	N	33	1	+									0	0	340	+	+	+	+			0	+C	0		+						160/80
7	+		F	W	62	1	+						+			0	0	330	+	0	Calcium	+			0	0	0	+	+	+					120/50
8	+		M	W	50	+	Dil. +				+						+	800	+	+			+		+	+	+		+	Sl.		+			NR
9	+		M	W	51	+	Dil. +				+						+	840	+	+	+	+			0	0	0		+						154/42
10	+		M	W	55	+	+										+	450	+	+		+			+	⟨+	+		+	+					160/60
11	+		M	W	52	+	+				+						+	600	+	+		+			+	+	+	+	+	+					154/46
12	+		M	Ch-N	43	2	Dil. +									+	+	790	+	+	+	+			NR	NR	NR	NR	+	Sl.					NR
13	+		M	W	59	10	Dil. +	+			+							450		+		+			+⟩	+	+		+			+			138/50
14	+		M	W	58	+	Dil. +										+	900	+	+		+			0	+C	0		+			+	+		130/42
15	+		M	W	37	+	Dil. +					+ Inter-Cardiac	+				+	NR	+	+	+	+			0	0	0		+						146/50
16	+		M	W	37	+	+										+	750	+	+	+	+	+		0	0	0		+						130/30
17	+		M	W	50	+	+				+		+				+	300	+	0	+	0	+		0	0	0		+			+			100/50
18	+		M	N	62	+	+					+				+	+	NR	+	+	0	+			+C	0	0		+						150/80
19	+		M	N	40	+	+	+						Sacc. +			Normal	350	0	0		0	0		0	0	0		+			+		+	140/78
20	+		M	W	60	+	+									+	+	620	+	+	+	+			0	0	0	+	+	+					150/76
21	+		M	W	62	2	+	+				Fusiform				0	0	310	0	0	0	0	0		0	0	0		+				+		120/70
22	+		M	W	52	5	+						+			0	0	NR	0	0	0	0	0		0	0	0		+	0		+			125/80
23	+		M	N	55	1	Dil. +										+	NR	+	+	+	+			0	0	0		+			+			180/56
24	+		M	N	35	+	+				+						+	550	+	+	+	+			+	+	Sl.		+			+			164/84
25	+		M	W	42	8	+	+				+				0	0	NR	+	+	+	+			+	⟨+	+		+						130/70
26	+		M	W	66	4	+										+	800	+	+	+	+			+⟩	+	+		+						NR
27	+		M	W	66	+	+					+	+			0	0	Normal	0	0	0	0	0	0	0	0	0		+			+			R 125/80 L 110/80
28	+		M	N	61	+		+	+						+	+		240	0	0	0	0	0	0	0	0	0		+					+	R 140/102 L 118/82
29	+		M	N	52	+	+				+			+		+	+	880		+	+	+	+		+	⟨+	+		+	+				+	140/68
30	+		M	W	60	3	+				+	Sacc. +				+	0	NR	+	0	+	+			0	0	0		+	+		+			144/66
31	+		M	N	44	+	Dil. +										+	520	+	+	+	+			No Stenosis		+		+			+			180/50
32	+		M	N	35	+	+										+	1050	+	+	+	+			NR	NR	NR		+			+			160/0
33	+		M	W	38	+	+	+									+	700	+	+	+	+			+	0	0		+						180/50
34	+		F	W	55	+	+				+						+	400	+	+	+	+	+		Calcium +		+	+	+	+					140/70
35	+		M	W	54	+	+				+						+	765	+	+	+	+	+		+	+C	+		+						115/80
36	+		M	W	55	+	+				+	+	+				+	NR	+	0	+	+			+	+	+		0	+	+				176/80
37	+		M	W	45	+	+					+					+	590	+	0	+	+			0	0	0		+						120/40
38	+		M	W	52	1	+				+						+	NR	+	+	+	+			+	+C	+		+	Sl.					120/60
39	+		M	N	25	+	+					+					+	550	+	0	+	+	+		+	+	+		+				+		130/0
40	+		F	N	35	+	+					+					+	NR	+	+	NR	+			+	+	+		+						NR
41	+		M	W	68	+	+	+			+	+	+	+				NR	+	0	+	0			0	0	0		+						NR
42		+	M	Ch	61	3	+			+						NR	NR	NR	0	0	0	0	0	0	0	0	0		+						240/110
43		+	M	W	45	+	+									NR	NR	NR	NR	NR	NR	0	0		+	0	0		+						NR
44		+	M	W	52	4	Dil. +			+	+					+	+	550	Fusion			0	+		0	0	0	+	+	+					190/120
45		+	M	W	67	+	+				+	Fus. +		Sacc. +		+	+	NR	NR	NR	NR	NR	NR		0	0	0	+	+	+					172/94
46		+	M	N	52	+	+			+	+					+	+	NR	0	0	0	0	0		0	0	0	+	+	+			+		225/160
47		+	M	W	51	1	+				+					+	+	500	0	+	0	0			+	0	0		+			+			90/70
48		+	M	N	83	2	+				+					+	+	500	0	+	0	+			+	+	+		+			+			160/65
49		+	M	W	47	+	+			+								420	0	0	0	0	0		0	0	0	0	+	0		+			146/92
50		+	M	W	60	+	+			+	+							260	0	0	0	0			+	+	(+)		+	Both		+			164/120
51		+	M	W	62	5	+			+	+					+	+	650	0	0	0	0	+		0	0	0		0	+	+	+			NR
52		+	M	N	68	3	Dil. +									+	+	640	+	0	+	0			0	0	0		+			+			150/90

\+ = Adequate period of observation (under Days in Hospital)
C = Complete closure (under Coronary Osteal Stenosis)
D = Denied (under Age When Chancre Appeared)
* Chart by Statistical Service of the New York Tuberculosis and Health Association.

TABLE IV* (*Continued*)

MUR-MURS			SEROLOGY			TREATMENT	AGE WHEN CHANCRE APPEARED	CAUSE OF DEATH					MICROSCOPIC EVIDENCE	DIAG. MADE CLINICALLY	DURATION OF SYMPTOMS	INITIAL SYMPTOM				REMARKS
Aortic Systolic	Aortic Diastolic	Austin Flint	Positive	Negative	Not Recorded			Heart Failure	Pneumonia	Myocardial Infarction	Rupture	Others				Dyspnea	Angina	Ankle Edema	Others	
+	+	+	4+			0	NR	+						+	4 yrs.				Cardiac	Aortic Cusps Calcified. Sudden Death in Sleep. Right Coronary Ostium Pinpoint
NR	NR	NR			+	0	D				+			+	1 wk.				Hemoptysis	Diagnosis made by House Staff
NR	NR	NR	4+			+	25	+						+	4 yrs.	+	+	+	PND	
+	+	+	4+			NR	NR		+					+	NR				NR	Aneurysm behind Cusp Myocardial Infarction
+	+	0	4+			+	47				+			+	3 wks.				Hoarseness	
NR	NR	NR			+	0	D					Coronary Insufficiency	0	+	1 wk.		+			
NR	NR	NR			+	0	NR	+				Pulmonary Edema	+	0	NR				NR	Calcific Aortic Disease. Aneurysm Circ. 10 cm.
+	+	+	4+			0	0		+			Cerebral Accident	0	+	4 mos.				Pain in Back	Patent Foramen Ovale
+	+	0		+		0	D	+					0	+	9 mos.	+		+		
0	+	0	4+			0	20	+					0	+	2 yrs.	+				
+	+	+	4+			0	D	+					+	+	7 wks.				NR	Occlusion of Rt. Innominate Artery by Mural Thrombus.
+	+	+	A/C			0	D	+					+	+	3 wks.	+				CNS Lues – Clinically
+	+	+	4+			0	40		+				0	+	2 wks.	+		+		Saccular Aneurysm of Splenic Artery with Calcification.
+	+	0	4+			+	24		+			Tbc.	+	0	3 yrs.	+				Diagnosis made by 2 Attendings. Hydronephrosis
+	+	0	4+			+	22					Pericarditis	+	+	14 wks.	+				
+	+	0		+		+	26	+					+	+	5 yrs.				NR	Aortic Valve Calcified. Sp. Fl. Wassermann Neg.
+	+	0	4+			+	0		+			Tracheal Compression	+	+	7 mos.	+	+		Cough	Ring narrowed. Commisures fused. Trachea compressed.
+	+	+	4+			+	D			+			+	+	11 mos.	+	+			Myocardial Infarction. Sino Thrombosis
+	0	0	4+			+	25		+		+		+	+	5 mos.	+			Cough	Rupture of Aneurysm into Left Main Bronchus. Erosion of Vertebra and Ribs.
+	+	0	4+			0	D	+					+	+	4 mos.	+	+	+		
+	0	0	4+			0	D					Pulmonary Tbc.	+	+	5 yrs.		+			
0	0	0	4+			0	Pos. Sero.	+	+				+	+	5 yrs.		+			
+	+	0			+	NR	NR		+				+	+	4 mos.	+				S.B.E. Aortic and Mitral Valves
+	+	0	4+			NR	?	+	+				+	+	10 yrs.	+			Palpitation	
+	+	+	4+			+	14	+				Pulmonary Edema	+	0	N R				NR	Compression of Pulmonary Artery by Aneurysm
+	+	+			+	0	NR	+					+	+	NR				NR	Gaucher's Disease
0	0	0	4+			0	32		+				+	+	4 mos.	+			Chest Pain Hoarseness	Paralysis Left Vocal Cord
0	0	0		+		0	D				+		0	+	1 yr.	+				Erosion T11, 12, L1, 2
0	+	0	±			0	D	+					+	+	NR				NR	Erosion of Manubrium. Aortic Stenosis and Calcification. Pulmonary Infarction
+	+	+	4+			+	D	+	+				+	+	4 yrs.	+				
+	+	+	4+			+	19	+	+				+	+	2 yrs.	+		+		
+	+	0	4+			+	D	+	+				+	+	1 yr.				PND	Right Coronary Cusp Torn
+	+	+	4+			+	D	+					+	+	11 yrs.	+		+		
0	+	0	±	K+		NR	NR	+					0	+	NR				NR	CNS Lues – Sp. Fl. Wassermann 4+. Cusp thickened and calcified.
0	+	0	4+			0	19	+					+	+	6 mos.	+		+		
+	+	0	4+			+	NR	+		+			+	+	3 yrs.				Chest Pain	Myocardial Infarction due to Coronary Thrombosis Sp. Fl. Wassermann 4+.
+	+	+	4+			0	D	+					+	+	6 mos.	+		+		
0	+	0			+	+	32	+					0	+	9 yrs.					Ruptured Cusp
+	+	0			+	+	NR	+					+	+	1 yr.				NR	
+	+	0	4+			NR	NR	+				Pulmonary Edema	+	+	3 yrs.					
0	0	0	4+			+	D					Suppurative Mediastinitis	0	+	2 yrs.	+	+			Compression of Left Main Bronchus. Compression of Oesophagus. Sp. Fl. Wassermann Neg.
0	0	0	±			NR	NR					Adenocarc. Kidney	+	0	None					Adenocarcinoma of Kidney
0	0	0		+		NR	NR					Hodgkin's Disease	+	0	None					Hodgkins Disease
0	0	0			+	NR	NR		+				+	0	NR				NR	Active Rheumatic Valvulitis. Fusion of Commissures.
0	0	0		+		0	D					Suppurative Pyelonephritis	+	0	None					Suppurative Pyelonephritis. Multiple small Aneurysms.
0	0	0		+		NR	NR					Miliary Tbc.		0						Miliary Tbc. Cancer of Prostate
0	0	0			+	NR	NR		+					0						Lobar Pneumonia
+	0	0	4+			NR	D		+				+	0	None					Pneumonia
0	0	0	4+			0	D		+				+	0	None					Granuloma of Lymph Nodes, Pneumonia
+	0	0	4+			0	D		+				+	0	None					Pneumonia
0	0	0			+	0	D			+		Rupture of Ventricle	+	0	None					Thrombosis of Both Coronaries. Rupture of Ventricle.
0	0	0		+		0	D	+				Pulmonary Edema	+	0	3 yrs.	+				Pulmonary Infarction

\+ = Adequate period of observation (under Days in Hospital)
C = Complete closure (under Coronary Osteal Stenosis)
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* Chart by Statistical Service of the New York Tuberculosis and Health Association.

ways comes from aneurysmal rupture. In tuberculosis of the lungs and in gastric lesions a single bleeding is seldom large enough to be fatal. Even esophageal varices seldom cause death at their first rupture.

Rarely, one has to differentiate between aneurysm and syphilitic bronchial stenosis. If stenosis occurs in the bronchus on the left side, diagnosis may be very difficult, as the left upper lobe is the site of the so-called "aneurysmal phthisis" described in the medical books of half a century ago and caused by bronchial compression by aneurysm. However, if there is no pulsation or decidedly accentuated aortic second sound, it is not likely that the collapse of the lung is on the basis of aortic aneurysm. Syphilitic bronchial stenosis, causing atelectasis in the right lung, has sometimes been confused because the traction of the right lung uncovers the aortic valve region, making the second aortic sound much more intense. Here again, pulsations are absent, and even if present to a slight extent ought not to confuse us as it is impossible to conceive of an aneurysm without a huge x-ray shadow compressing the right bronchus sufficiently to obstruct it.

Roentgenologic studies may give information in revealing an aneurysmal shadow, the border of which may be seen to pulsate violently on fluoroscopy or by the roentgenkymogram. Esophageal studies may show displacement of this tube by the aneurysm. The bronchoscopist, in our experience, has been more misleading than helpful; pulsations of the bronchial wall have been ascribed to adjacent aneurysm when they were actually due to a tumor mass transmitting a normal aortic pulsation.

Many points stressed in this section may seem ultra-refined or even purely theoretical to many readers. On the contrary, most of them, especially those touching on differential physical diagnosis, are the ones most discussed on ward rounds when problems of cardiac diagnosis are encountered.

In our final classification of these cases as presented in tabulated form we transferred one case from the primary to the incidental group (Case 52). A case of completely uncomplicated aortitis, it could not possibly have caused hypertrophy of the heart to a weight of 640 Gm. Consequently, the syphilitic aortitis is considered incidental here to hypertensive cardiovascular disease. Death occurred from pulmonary edema following pulmonary thrombosis and infarction.

Of the forty-one cases now left and listed in the primary group, the clinical diagnosis was confirmed by autopsy in thirty-seven (90 per cent). Two other cases were correctly diagnosed, one by the house staff and the other by two visiting men, though they were not accepted officially, bringing the total recognized by some member of the staff to 95 per cent.

Aortic valvular insufficiency was present in thirty-one cases and was recognized through its diastolic murmur in twenty-seven of twenty-eight cases recorded. In one case a diastolic murmur was recorded but the pathologist reported no aortic valvular insufficiency.

We did not fare so well with aneurysms which were present in twenty patients. Of these we detected only twelve, confirming the statement that "a large proportion of aneurysms are first recognized at the autopsy table."

While not germane to the subject under discussion, a glance at the listing in the footnote* will reveal what a rich field of study chronic disease offers, and how in even a small group of cases, apart from curiosities and rarities, careful tabulation and analysis may uncover definite evidence, often carelessly overlooked, which will force us to revise our concepts. In the first place, in the symptomatic group coronary thrombosis with myocardial infarction, though

* Unusual or interesting findings revealed at postmortem in forty-one cases of primary syphilitic aortitis

present in slightly less than 5 per cent of the cases, comes out of the "never" category into which, through our clinical impressions too long unchecked by facts, we have lately been placing it. More important is the discovery that coexistent syphilitic aortic valvular insufficiency and aortic stenosis which we have long held to be incompatible on theoretical grounds, can and do coexist, as they did to the extent of 12.5 per cent (four cases). One hates to think of the number of generations of medical students to whom each year with increasing fluency due to repetition—and with a slight trace of condescension and superiority—we have proved with the brilliant logic of a medieval churchman what isn't so.*

DIAGNOSIS OF ASYMPTOMATIC SYPHILITIC AORTITIS

A good introduction to the discussion of the diagnosis of syphilitic aortitis in its latent or asymptomatic phase, is the admission that irrespective of our diagnostic attainments with syphilitic aortitis in its stage of clinical expression, in the eleven cases in which it was a casual finding at autopsy in patients who were literally sick unto death, we never even suspected its presence. As three of our patients showed strongly positive serologic reactions, we should at least have risked a guess in these cases.

Because in syphilitic aortitis there is a latent or asymptomatic period usually of many years' duration, clinical interest naturally centers around the diagnosis of the lesion in this stage, which has been variously called "early" or "uncomplicated" syphilitic aortitis. However, on recalling the cases cited by Albutt of deaths in the early twenties from syphilitic aortitis complicated by coronary ostial stenosis, one pauses before becoming dogmatic in stating either the decade in life or the number of years after a chancre during which we may presume to find "uncomplicated" aortitis; the best we can do is to try to detect cases of syphilitic aortitis while the disease is still latent (i.e., asymptomatic), and hope that in some of them the process is still "uncomplicated" by coronary ostial stenosis, insufficiency of the aortic valve or aneurysm. Theoretically, the recognition of aortitis in the asymptomatic stage is essential if we are to achieve truly preventive medicine, for by the time patients present symptoms they are *never* in the stage of "uncomplicated" syphilitic aortitis, and furthermore, in the majority of them, because of the inroads the disease has made by this time, their remaining span of life is relatively brief.

This statement is a challenge to the validity of the criteria for the diagnosis of uncomplicated aortitis set up by the United States Public Health Service and a group of cooperating syphilis clinics. These criteria, which were published in 1932 by Cole, were as follows: (1) Teleroentgenographic and

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in the symptomatic stage:

	No. Cases
Right ostial stenosis and myocardial infarction (sine thrombosis)	1
Coronary thrombosis with myocardial infarction	2
Calcific aortic valvular disease (aortic stenosis superimposed on syphilitic aortic valvular insufficiency)	4
Calcific aortic valvular disease (aortic stenosis), no syphilitic involvement of valve	1
Ruptured aortic cusps	2
False aneurysm in sac of ascending arch	1
Intracardiac aneurysm	1
Aneurysm compressing left auricle and pulmonary artery	1
Circoid aneurysm of both carotids	1
Aneurysm of splenic artery with calcific infiltration	1
Subacute bacterial endocarditis engrafted on aortic syphilitic valvulitis	1
Patent foramen ovale	1
Stenosis of mouth of innominate artery by arteriosclerotic plaque causing reduction in size of pulse and blood pressure in right brachial	1
Gaucher's disease	1

* In this pathologic picture, the commissures are widened by the syphilitic process. Then both the ring and cusps are infiltrated with calcium which so stiffens the cusps, especially at their bases or line of attachment to the ring, that the force of the blood against them in systole can raise them but little, with a resultant stenosis of the valve.

fluoroscopic evidence of aortic dilatation; (2) tympanitic bell-like tambour accentuation of the second aortic sound; (3) a history of circulatory embarrassment; (4) increased retromanubrial dullness; (5) progressive cardiac failure; (6) substernal pain and (7) paroxysmal dyspnea. In the same article this list is preceded by the statement that "Every effort should be made to recognize the existence of syphilitic cardiovascular involvement while in the stage of uncomplicated syphilitic aortitis, before the development of irreparable anatomic or functional damage to the heart."

Now, every case of narrowing of the coronary ostium is not only a complication of syphilitic aortitis, but a serious complication. Yet, how can patients with syphilitic aortitis, who have no aortic valvulitis or aneurysm, give "a history of circulatory embarrassment"; show "progressive cardiac failure"; have "substernal pain" or "paroxysmal dyspnea" on the basis of a syphilitic process, except through narrowing of one or both coronary ostia? On the other hand, if we are really talking about *uncomplicated* aortitis (i.e., without coronary ostial narrowing, aortic valvulitis or aneurysm), what in the pathology of aortitis *per se* can cause symptoms of impairment of the coronary circulation or of cardiac function? The answer, of course, is nothing.

In progressive narrowing of a coronary ostium, until the volume of blood flowing through the coronary artery is reduced to a point where there is the characteristic electrocardiographic response to an anoxemic test, there is no way of determining the presence of ostial stenosis. By that time the initiation of the symptomatic phase is usually imminent. Occasionally, the presence of coronary ostial stenosis is dramatically revealed during a course of antisyphilitic treatment by a "therapeutic reaction" in which edema around the coronary orifices is sufficient to cause temporary closure. Such accidents have at times terminated fatally.

There is no constant correlation of the degree of narrowing in the ostia with the initiation of symptoms. The rate at which the stenosis proceeds is probably a factor, its slow progress favoring the development of a more or less adequate collateral circulation. The extent of the other sources of myocardial blood supply in all likelihood determines the degree of ostial narrowing for which a collateral circulation can compensate. In cases of death from non-syphilitic causes, atresia of both coronary ostia from syphilitic aortitis, as an incidental finding, has been recorded. Since coronary ostial stenosis cannot be diagnosed prior to the beginning of symptoms, criteria for the detection of uncomplicated aortitis which include symptoms of dysfunction are not only unsound but, by their inclusion of symptoms of impairment of the coronary circulation, are even dangerous, as they fail to warn the general practitioner of the hazards inherent in the treatment of syphilitic aortitis when coronary ostial stenosis is present. Physicians should be taught that paroxysmal dyspnea and angina pectoris are symptoms of impairment of the coronary circulation; so that on meeting them in their patients with apparently uncomplicated syphilitic aortitis, they will realize that they are dealing with a lesion of the coronary arteries in which careless therapy may cause serious and even fatal reactions. The most we can strive for is the detection of syphilitic aortitis in its asymptomatic stage. In any case discovered we can only hope that there has been no invasion of either coronary ostium. There are not many figures available to aid us in determining statistically the likelihood of that hope being realized. Most studies based on necropsy findings have not separated their latent from their symptomatic group. In our Bellevue series the number of cases of asymptomatic

syphilitic aortitis is too small for any general conclusion to be valid. However, coronary ostial involvement occurred in 27 per cent, as compared with over 50 per cent of the symptomatic group. It is interesting to note that in the incidental group uncomplicated aortitis existed in 63.5 per cent of the cases, even though their ages ranged from the fourth through the sixth decades. Also, based on our experience even with the symptomatic group, one may assume that without symptoms of cardiac failure, in aneurysms distal to the ascending portion of the aortic arch, the percentage of cases showing coronary ostial involvement is relatively small. Of these seven cases, in none was ostial stenosis present, and of the remaining thirteen aneurysms of the ascending arch, six showed no ostial stenosis.

In the absence of evidence of aortic valvulitis or aneurysm, what are sound criteria for assuming the presence of latent syphilitic aortitis? In presenting them, we must realize that they are valid only if the patient has not yet reached the end of the fourth decade and shows neither evidence of arteriosclerosis nor hypertension. With these restrictions, we may say that if on auscultation we hear an accentuated aortic second sound of low pitch and of so-called tambour quality, we should suspect syphilitic aortitis. If, in addition, even without definite radiographic evidence of aortic dilatation, the ascending arch in some positions shows exaggerated pulsations on fluoroscopy our suspicion is strengthened; and if also we can hear even a faint systolic murmur in the right second interspace near the sternum, our suspicion increases in geometrical proportion. If dilatation of the arch is undoubtedly present, the diagnosis is almost certain; with a history of syphilis or other supporting physical evidence, such as a positive serologic finding, it is definite. Obviously, we shall detect it in this stage only as an incidental finding during a routine examination and then only if sufficiently alert to search for it. The evaluation of these different signs and laboratory aids have different weights at different ages of life. In the second and third decades, the quality and accentuation of the second aortic sound has much greater diagnostic significance than later, and if found in conjunction with dilatation of some part of the aortic arch as revealed by a faint basal systolic murmur, it may be considered evidence of syphilitic aortitis, even without a positive serologic reaction. On the other hand, in the later decades, a strongly positive serologic reaction is of especially great weight when the dilatation of the aorta may be caused by either arteriosclerosis or hypertension, which also may obscure or change the quality of the second sound. In seven of the eleven cases in the older age group in which syphilitic aortitis was an incidental finding and was truly "uncomplicated," three showed a strongly positive serologic reaction.

The general practitioner will rarely have much opportunity for detecting aortitis at this stage, though in recent years certain medicosociologic trends have increased the possibilities of early diagnosis through uncovering latent infection. Among these are premarital Wassermann tests, tests in pregnant women and pre-employment medical examinations, many of which include both blood Wassermann tests and chest x-rays. The greatest opportunity today exists in the numerous syphilis clinics throughout the country; but, as at present conducted with insufficient personnel and few skilled internists, there will be relatively few patients in whom this condition will be recognized. That they are probably fairly numerous is shown by the report of McDermott et al. from the Syphilis Clinic at New York Hospital where, over a four and a half-year period, from October, 1936, to April, 1941, syphilitic aortic valvulitis was found in 3.6 per cent of the 2,718 syphilitic patients

examined. The tragic aspect of this report is that of ninety-one of these patients reported on, who did not have aneurysm in addition, 51 per cent had already proceeded to the symptomatic stage. Certainly, in endeavoring to detect more* of these patients in the latent period, greater emphasis should be placed on the importance of every physician including a blood Wassermann test as a part of his general examination of each new patient, irrespective of the condition for which relief is sought. In New York City, where such examination imposes no additional financial burden on the patient, failure to carry out this test is little short of medical negligence. It should be included also, together with a roentgenogram of the chest, as a routine part of a periodic health examination. It is now generally conceded that slight degrees of aortic widening cannot be detected by x-rays. Widening of the ascending portion of the arch may be presumed if that portion of the aorta shows an accentuated curve in the x-ray silhouette. This can best be seen on a film taken in the left eccentric position. With associated hypertension or arteriosclerosis, this dilatation is in no way specific.

In all probability, even if physicians are on the alert to detect the presence of the stigmas of syphilitic disease, the recognition of cardiovascular syphilis at the stage when the disastrous effects of its progress may be prevented is likely to be too difficult to be of practical value on a large scale. Another important factor contributing to the difficulty in recognizing asymptomatic aortitis is the lack of knowledge among many patients of their having had a chancre. Members of the low-income groups rarely seek advice except when seriously ill and usually do not come under medical observation until after symptoms begin.

Any hopes for lessening its frequency must rest on: (1) Reduction of the incidence of syphilis through public health measures which at present are grossly inadequate from an epidemiologic point of view and (2) more thorough and efficient treatment of syphilis following its initial appearance and through the secondary stage of the disease. Otherwise, cardiovascular syphilis will continue to be a distinct problem of medicine and an important cause of death.

There is again need of another cooperative study based on the evaluation of diagnostic criteria. At the same time, stricter criteria for pathologic diagnosis are necessary if we are to hope for greater accuracy in correlating clinical pictures with pathologic findings.

Criteria for the diagnosis of uncomplicated aortitis should be dropped, as it is impossible in the asymptomatic stage to rule out some coronary ostial narrowing. The term "uncomplicated" aortitis, if used, should refer in a pathologic classification to those cases without coronary ostial stenosis, aortic valvulitis or aneurysm. In the majority of cases examined at postmortem, the presence of syphilitic aortitis and its complications can be proved without difficulty, and in cases without atherosclerosis an acceptable diagnosis can be made based on the characteristic gross findings in the lesion and in its complications. On occasion, the association of decided atherosclerotic changes in the aorta itself around the coronary ostia or in the aortic valve affecting both the ring and cusps may so confuse the situation that one may not be sure whether the case is a combination of syphilis and atherosclerosis or atherosclerosis alone. Certain criteria should be set up as minimal requirements for classifying as syphilitic cases in which

* One unexpected finding in our Bellevue group was the extraordinarily small percentage of asymptomatic cases. Does this mean that only 20 per cent of the cases of syphilitic aortitis fail to reach the stage of symptomatic expression, or does it mean that pathologists fail to recognize it in many instances when it is an incidental finding? That only eleven cases were recorded in seventeen years would suggest the latter, but the caliber of the work in the Department of Pathology is against it.

atherosclerosis obscures the pathologic picture. However, we should bear in mind that when the type of clinical syndrome strongly suggests syphilis, or when there is a history of or physical evidence for a syphilitic infection, and when the serologic reaction is strongly positive, these factors should be allowed to influence a pathologic decision even if the histopathologic evidence results in the Scotch version "not proven."

In those cases in which the diagnosis is in doubt, sections taken within 1 cm. of the coronary ostia, aneurysm or aortic ring should at least have these minimal findings to permit the classification of the lesion in the ostia, aortic valve or aneurysm, respectively, as syphilitic. Syphilitic ostial stenosis and coronary artery thrombosis rarely coexist; and syphilitic aortic valvulitis rarely invades the leaflets without involving the ring and widening the commissures. Therefore, in the first instance with coronary artery thrombosis present, the section should be taken through the ostium instead of within 1 cm.; and in the second instance, especially if the commissures are described as "fused," sections showing the criteria for syphilis should be required either through the commissural area or leaflet unless, of course, there has been calcific infiltration. These histopathologic criteria, which have been kindly furnished by Drs. Von Glahn and Spain, Director and Associate Pathologist, respectively, of the Department of Pathology at Bellevue Hospital, are as follows:

There should be present a perivascular infiltration of lymphocytes or plasma cells in the adventitia with or without endothelial cell proliferation of the vasa vasorum. The section should show some disruption of elastic tissue fibers in the media, even though minimal, with or without definite stellate vascularized scars. Fibrosis of the intima need not be present to make a definite diagnosis of syphilitic aortitis.

Unless criteria can be established under which no case with bizarre findings can be classified as syphilis except on properly supporting evidence, our statistics will have little meaning, and our actual knowledge of the amount of unusual combinations, such as aortic stenosis and syphilitic valvulitis, and coronary thrombosis and coronary ostial stenosis, will remain purely speculative.

PROGNOSIS OF AORTITIS AND ITS COMPLICATIONS

In considering the outlook for patients with syphilitic cardiovascular disease, there are a number of factors influencing its course and duration. Of these by far the most important is the presence or absence of symptoms. In the asymptomatic stage we have no good yardstick by which we can measure the progress of the disease up to the time we encounter the patient, and consequently we have no estimate of the reserve which may be drawn on before its depletion leads to symptoms of beginning breakdown. As so many patients do not admit having had syphilis, we have little more than an even chance of learning when the syphilitic infection started, and without this we cannot even apply the law of averages to our estimate of the time at which it may show symptomatic expression. On the other hand, in the symptomatic phase we have acquired a fairly accurate estimate of its duration and outcome.

In order to help one another to obtain more knowledge about syphilitic aortitis we must first straighten out our thinking by eliminating meaningless and ambiguous terms we have used loosely and interchangeably in the past. We may properly speak of uncomplicated syphilitic aortitis as an incidental lesion found at autopsy; we cannot use the term as indicative of a pathologic state which has its recognizable clinical syndrome in the living. For, though we may have under consideration a patient in whom

we have detected the existence of even the minimal amount of aortitis that can be discovered by the employment of every modern diagnostic technic, at present we have no means of ascertaining whether the aortitis has invaded the coronary ostia until the patient is practically at the beginning of his symptomatic phase. The term "early" is ambiguous and misleading in that it has often been used interchangeably with "uncomplicated." Furthermore, from the common meaning of the word, it has an underlying implication when used in connection with syphilitic aortitis that there is some correlation between the duration of the disease and its rate of progress. For all we know, a patient with cardiovascular syphilis may carry any one of its complications for many years before symptoms ensue.

In the symptomatic phase of aortitis, prognosis for duration of life is bad. In insufficiency of the aortic valve, death usually occurs within two years from the onset of symptoms and the course is usually shorter when ostial stenosis is associated. In aneurysm the outlook on the average is the same as for these other two conditions, but there is much greater individual variation, as some patients live for from five to ten years after the onset of symptoms; here again, coexistence with either valvulitis or coronary ostial stenosis, or both, hastens the progress. Life is usually much shortened after an aneurysm has caused constriction of the lumen of a bronchus, as pulmonary suppuration soon follows.

Antisyphilitic treatment, if at all effective in the symptomatic group, prolongs life by only a few months when there is coronary artery or aortic valvular involvement. In aneurysm, gains up to two years or more have been recorded in treated cases as compared with untreated groups. The outlook is greatly improved with that group of cases in which, in addition to antisyphilitic treatment, electrocoagulation can be carried out by wiring in the aneurysmal sac. In cases in which, in addition to wiring, the progress of the syphilitic process has been permanently arrested through effective antisyphilitic treatment, brilliant results have been obtained.

Another important factor which has a great influence upon prognosis is race. (Tables I and II.) The Negro seems to develop symptoms earlier in life and to run a more rapidly progressive course; and he is more likely to show a greater percentage of combined complications. For example, in our Bellevue series, while Negroes comprised 29 per cent of the total cases studied at autopsy, 67 per cent of them showed symptoms before the age of fifty, as compared with 21 per cent in the white group; and 67 per cent died before the age of fifty, as compared with 18 per cent of the white group.

In respect to aneurysm, while Negroes comprised 29 per cent of the Bellevue cases, they accounted for 23 per cent of aneurysms; and while none of the white group having aneurysm died before the age of fifty, 50 per cent of the Negroes succumbed.

Aortic insufficiency was present in 68 per cent of the white patients and in approximately 83 per cent of the colored; 33 per cent of the white cases died before fifty, as compared with 75 per cent of the colored.

The combined lesions of coronary ostial stenosis, aortic insufficiency and aneurysm were present in seven patients; of these, 57 per cent were colored, but this accounted for 33 per cent of the colored group, as compared with 10 per cent of the white group. Only 33 per cent of the white group with this triad of complications showed symptoms or were dead before the age of fifty, while 50 per cent of those in the colored group had become symptomatic by that age, and one had lived beyond the fifty-second year.

In considering the outlook for patients

once their aorta is invaded by the syphilitic process, one speculates as to the percentage in whom the process will remain uncomplicated or at least asymptomatic throughout life. Its frequency as an incidental finding at autopsy might be some clue if we had sound criteria of diagnosis for detecting the syphilitic lesion and were sure that careful search would be made for its presence. It is rather impressive that only eleven cases of incidental asymptomatic syphilitic aortitis were found at autopsy in seventeen years, but even more so that 63 per cent of these were still uncomplicated though in the older age group.

Our knowledge of the variations in the life span of patients with syphilitic aortitis, as measured from the time of the initial infection, is of no value when applied to a patient found in the latent stage. This knowledge is based almost exclusively on studies of patients presenting themselves for treatment because of symptoms. Obviously, in the asymptomatic individual, without evidence of aortic valvulitis or aneurysm, we cannot figure even approximately how many years the patient will live. We can well assume, though, that we can roughly estimate the degree of activity and severity of a syphilitic process by comparison of the amount of damage found with the time during which the process has been operating. Its virulency may be assumed to be in inverse proportion to its duration and proportionate to the degree of damage revealed on examination. This is, of course, without consideration of the malign influences potential in any hidden coronary ostial involvement, a lesion present in a large percentage of cases. Obviously, signs of any involvement of the ascending portion of the aortic arch increases materially the risk of serious developments. Also, when aortic valvular insufficiency is present, even though asymptomatic, the hazard is increased in proportion to the degree of valvular leakage and the amount of cardiac enlargement present. Even if treated, cardiac failure may ultimately ensue though postponed by the arrest of the syphilitic process. There is always an uncertain and serious potential factor in all cases of syphilitic heart disease, even in the latent stage. Martland reported that of the cases autopsied in his Medical Examiner's Office in which sudden death had occurred, of those in which heart disease was responsible, 33 per cent were due to syphilis. Of these, aortic insufficiency was rated as being most frequently responsible, and aneurysm with rupture of next importance. There is no careful analysis of the degree of coronary ostial stenosis present in those patients with aortic insufficiency who died suddenly. This lesion presents another hazard, which is the possibility that in overzealous treatment for syphilis, it may be responsible for sudden death from heart failure or pulmonary edema.

One aspect of prognosis of which we have little knowledge is the percentage of asymptomatic cases which are likely to remain so or the percentage in which "uncomplicated" aortitis will not progress to the stage of either aneurysm, coronary ostial stenosis or aortic insufficiency. One cannot assume after an analysis of our own fifty-two cases that they are representative of the community in general. The sample is altogether too small. It is interesting to note, however, that of the eleven cases of incidental syphilitic aortitis, seven of them were entirely uncomplicated, and these ranged from the fourth through the seventh decade. Any cooperative study should make this one of its chief interests, and with a re-definition of "uncomplicated" one may hope to get some valuable information.

TREATMENT OF CARDIOVASCULAR SYPHILIS

In planning the treatment of a patient with syphilitic aortitis, we must remember

that we have no way of detecting coronary ostial involvement or the degree of stenosis present in the asymptomatic stage of syphilitic aortitis. Therapeutic reactions in syphilitic involvement of the coronary orifices can produce alarming and even fatal results in rare instances. Consequently, antisyphilitic treatment of patients with aortitis should be started with caution. In view of the fact that we have seen three cases of serious reactions attributed to bismuth therapy in the last decade,* it is possible that starting treatment with as little as 0.1 Gm. of oil-soluble bismuth may in rare instances be dangerous. This is especially true of patients who already have symptoms of serious heart disease when greater caution in starting treatment must always be observed. This note of warning is sounded because a great deal of oil-soluble bismuth is sold and presumably used by the general practitioner. Incidentally, even doses of 100 mg. do not maintain effective levels given once every five to seven days. In starting treatment with bismuth the physician should remember that water-soluble preparations are absorbed and excreted rapidly. According to Cole, Sollmann and Henderson (1939) injections of water-soluble bismuth such as sodium bismuth tartrate or iodobismitol must be given at least three times a week to maintain a urinary excretion around 2 to 4 mg. of bismuth daily. Oil-soluble preparations such as bismocymol and biliposol should be given twice a week, while the insoluble preparations of bismuth salicylate in oil can be given once a week. One cc. of 10 per cent emulsion of bismuth subsalicylate in oil (125 mg. metallic bismuth) will usually give a daily excretion of from 3 to 4 mg. of bismuth. The absorption of the insoluble preparations is slower than of soluble bismuth, and in starting the treatment of cardiovascular syphilis this is an advantage.

It is advisable to start treatment of all patients with uncomplicated syphilitic aortitis with bismuth rather than the more actively spirocheticidal drugs, such as arsenicals or penicillin. As yet we have too little knowledge regarding the treatment of cardiovascular syphilis with penicillin to discuss it intelligently. Such treatment at present is experimental and must remain so for some time.

In the last few years a fair number of patients considered clinically (without autopsy) to have cardiovascular syphilis have been given, on medical wards, intensive penicillin therapy for acute infectious processes, especially pneumonia, without manifesting any obvious therapeutic reactions. The number coming under the writer's personal observation is too small to permit the drawing of any conclusions, but it does bear out the experience of Evan W. Thomas et al. who at present are employing penicillin in the intensive treatment of syphilitic cardiovascular disease. Here there has been some protection afforded by the employment of bismuth prior to the use of penicillin.

Past experience with bismuth and arsenical drugs indicates that our motto for successful treatment must contain these two apparently incompatible terms: "caution" and "courage"; caution to avoid "therapeutic reactions," and courage to employ arsenical therapy despite its well known dangers. Of late years, most cardiologists have relied more and more on bismuth exclusively for the control of syphilitic aortitis. The syphilologists, however, seem to favor the use of arsenicals as well, and it seems to the author that the weight of evidence is in their favor. The weight of evidence seems to indicate that it is doubtful whether syphilitic aortitis will be permanently arrested unless arsenical therapy is included in any course of thorough

* Two cases cited by Dr. I. Ogden Woodruff. One case cited through courtesy of Dr. Charles Nammack, Director of the Fourth Medical Division, Bellevue Hospital.

and prolonged treatment. Furthermore, to be effective, arsenical drugs must be given in reasonably adequate dosage. It is wise to start arsenicals cautiously with small doses but, if tolerated well, the dosage should be increased to effective therapeutic levels such as 0.04 Gm. or even 0.06 Gm. of arsenoxide. The arsenical of choice is arsenoxide (mapharsen, chlorarsen or similar preparations) because experience has proved that this is less toxic than any of the other arsenic derivatives now available.

The course of treatment in uncomplicated aortitis should cover at least two years. After any such course of treatment, the patient should be examined every six months with a view to determining either the recurrence of syphilitic activity or any evidence which would suggest further progress in cardiac or vascular damage. Treatment should be initiated with a course of bismuth therapy extending over a period of at least eight or ten weeks. If bismuth salicylate in oil is used, injections can be given every three or four days if the initial doses are less than 0.1 Gm. If well tolerated, however, the dosage should be increased to 0.2 Gm. each week. Following this, arsenoxide should be used, starting with 0.03 Gm. and increasing the dosage to 0.04 Gm. or 0.06 Gm. each week. If lower doses are used, treatment should be given oftener than once a week. Alternate courses of bismuth and arsenoxide over a two-year period are advisable. Each course of bismuth and arsenoxide should extend for a period of from eight to ten weeks.

In the symptomatic phase the same procedure can be carried out, save greater caution needs to be observed, especially when treatment is first started. If cardiac failure is present, compensation should be restored without any antisyphilitic therapy during this period, except the use of iodides. When the patient is no longer in heart failure, bismuth should be started in small doses and the first course should be extended for at least ten to twelve weeks. Arsenical drugs should be started with great caution, and the patient should be questioned at each visit as to tolerance. Any reactions should be regarded as dangerous and arsenical drugs stopped if they occur. In patients with symptomatic syphilitic heart disease it is always more important to treat the heart disease than the syphilis. No antisyphilitic treatment will repair damaged heart valves or make the coronary ostia more patent once scar tissue has already formed. Cardiac failure is handled as cardiac failure is under all conditions.

Digitalis is indicated, and the patient should be kept on maintenance doses. If any idiosyncracy seems to be present, better results are sometimes obtained by employing one of the glucosides, such as digitoxin, until cardiac compensation is restored. Bed rest is needed, and during this period of decompensation diminished fluids and a low-salt diet should be routine. As a matter of fact, both of these procedures are necessary even after compensation is established. If decided right-sided failure is present, a mercurial diuretic may be of help and may be given up to two or three times a week. In some cases ammonium chloride in doses of 1 Gm. three times a day may increase the effectiveness of the mercurial. However, we have found that the prolonged use of ammonium chloride is apt to cause gastric disturbance, and consequently we avoid its use when possible. Occasionally cardiac failure expresses itself in the form of an abrupt onset of pulmonary edema. An attack of this nature demands prompt action with bloodless phlebotomy with tourniquet, morphine, oxygen with a pressure mask, aminophyllin and mercurial diuretics. In our own experience since the pressure mask has been available, this procedure is so much more dramatically effective than any of the other measures which

have been used that pulmonary edema will at times rapidly subside by the use of this measure alone. It may be used with oxygen concentrations up to 85 per cent. Attacks of paroxysmal nocturnal dyspnea which come on early in heart failure may be helped by the use of an oxygen mask with about 50 per cent oxygen concentration.

Anginal pain is first to be treated by bed rest. If not sufficiently influenced, nerve block should be our treatment of choice. Neither oxygen nor nitroglycerin is particularly effective in controlling it. Our only other measures are the narcotics, and with their use there is great danger of establishing addiction. A fairly common and annoying complication of nerve block is a neuritis which sometimes lasts for two or three weeks, although usually not for more than a few days. Rarely a pneumothorax is produced during the procedure. For the relief of either pain or dyspnea occurring in aneurysms either eroding bone or compressing the trachea or bronchus, the only humane method is to give sufficiently large doses of narcotics to dull the patient's suffering, irrespective of their constitutional effects.

During the early course of the treatment of either aneurysm or aortic insufficiency in the symptomatic phase, sufficient attention has not been paid to the benefit of bed rest. In the case of aneurysm, a reduction in cardiac rate of 10 beats per minute eliminates over 14,000 beats a day with a proportionate relief of strain on the aneurysmal wall. Similarly, in aortic insufficiency, cardiac failure may be prevented by limiting the work of the heart through bed rest during the first few months of therapy. For example, in ostial stenosis in which the syphilitic activity is in the process of arrest under treatment, permanent cardiac failure may possibly be prevented through bed rest until a greater degree of collateral cardiac circulation for the heart muscle is developed. This is not merely an academic question; occasionally at autopsy we have seen hearts with almost complete occlusion of both coronary ostia in cases in which, from the history, there had been a fair degree of functional efficiency long after considerable ostial stenosis had been present.

Before leaving the subject of the treatment of aneurysm, one should comment on the improvement in technic which makes highly desirable wiring with electrothermic coagulation of sacculated aneurysms whenever their situation makes them available for surgical approach. Combined with antisyphilitic therapy, brilliant therapeutic results have been achieved. We should realize that competence in this branch of surgery is rare. In the symptomatic stage of the disease when cardiac failure is present, especially in patients in the lower economic group who cannot protect themselves satisfactorily from severe stress and strain except when in the hospital, the fight is a losing one. Gradually the free intervals between hospitalization become shorter and the period of hospitalization longer, until death supervenes from progressive cardiac failure.

SUMMARY

1. Cardiovascular syphilis is reviewed with especial reference to aortitis and its complications—coronary ostial stenosis, aneurysm and aortic valvular insufficiency.

2. The incidence, pathology, clinical manifestations and differential diagnosis of these complications are discussed in detail, together with prognosis and treatment.

3. In syphilitic aortitis, attention is drawn to the long latent or asymptomatic period and to the attempts to establish criteria for its detection before the appearance of symptoms.

4. The relationship of the complications of syphilitic aortitis to its symptomatic expression, and the prognostic significance of symptoms is discussed.

5. Cases are cited of coexistent pathologic entities usually defined as incompatible or non-occurring, i.e., stenosis of the aortic valve with syphilitic aortic valvular insufficiency, and coronary ostial stenosis with coronary artery thrombosis.

6. Present criteria for the diagnosis of "uncomplicated" aortitis are analyzed.

7. The frequency of coronary ostial stenosis is discussed, with special reference, based on the doctrine of probabilities, to the accepted method of initiating antisyphilitic therapy in the third stage of the disease.

8. A brief outline of therapy for cardiovascular syphilis is presented.

9. The clinical and pathologic data in fifty-two autopsied cases of syphilitic aortitis from the wards of the Medical Service of the First Division, Bellevue Hospital, are analyzed and cited in connection with various sections of the article.

CONCLUSIONS

1. In its symptomatic phase, syphilitic aortitis can be recognized clinically in a high percentage of the cases seen on an inpatient hospital medical service.

2. The possession of a high "index of suspicion" and the willingness to give careful attention to the finer points of differential diagnosis are prerequisites for its accomplishment.

3. Syphilitic aortic valvular insufficiency and aortic valvular stenosis, when caused by infiltration of calcium, are not incompatible.

4. Asymptomatic aortitis incidentally associated with other diseases requiring hospitalization will seldom be recognized, especially if the aortitis is "uncomplicated." A strongly positive serologic reaction in the upper age group should arouse suspicion of its presence.

5. In syphilitic aortitis, once symptoms of cardiac failure or of impairment of the coronary circulation appear, the outlook is gloomy, even with adequate treatment, not only for symptoms, but even for any appreciable extension of the life span. Selected cases of aortic aneurysm offer a more favorable prognosis.

6. The immediate outlook for any material reduction in the percentage of cases of syphilitic aortitis which will go on to symptomatic expression is discouraging. The general practitioner will see relatively few cases and will recognize fewer, especially if the prevailing neglect of routine serologic tests continues. So far there is little evidence of any trend toward that integration with the medical services which would ensure examination of patients by men trained in cardiology. Until authorities provide sufficient funds to employ personnel to do a decent epidemiologic job, the incidence of syphilitic infections and of unrecognized and untreated cases will remain high. During this period we may possibly offset the unsatisfactory situation by more extensive employment of rapid penicillin therapy to reduce the duration of infectiousness of syphilis.

7. Uncomplicated syphilitic aortitis is a pathologic entity incapable of producing symptoms; and there are no criteria for its diagnosis which can rule out a moderate degree of ostial stenosis of one or both coronary arteries.

8. Consequently, as uncomplicated syphilitic aortitis has no diagnosable clinical counterpart, criteria for its diagnosis should be discarded and criteria established for the diagnosis of latent (asymptomatic) aortitis without aneurysmal or aortic valvular involvement. This would be of practical importance clinically and would eliminate much present confusion and misunderstanding.

9. Stricter criteria for pathologic diagnosis are also necessary for atypical cases, though they should be sufficiently rigid in all cases to exclude wishful thinking.

10. When these criteria are accepted, a new cooperative study is desirable to correlate clinical and pathologic data on a sound basis. To be of value, the cooperating clinics must have the services of adequately trained cardiologists with in-patient hospital affiliation to insure proper observation of the patient throughout the natural history of his disease from the time of its detection.

11. Because of the unsound criteria established for the diagnosis of "uncomplicated" aortitis, the general practitioner must be re-taught that in syphilitic aortitis, symptoms of impairment of the coronary circulation mean coronary ostial stenosis.

12. Coronary ostial stenosis was present with sufficient frequency in our Bellevue Series to warrant assuming, on a statistical basis, that one is likely to meet it in any case of syphilitic aortitis, especially if the ascending arch or aortic valve is involved.

13. We believe, contrary to most syphilologists, that serious and even fatal Herxheimer reactions have occurred in cases of aortitis with coronary ostial stenosis by the initiation of treatment with the dosages of bismuth at present routinely employed and advocated.

14. The presence of coronary ostial involvement or even stenosis cannot be recognized in the asymptomatic phase.

15. Therefore, in all cases of syphilitic aortitis in which the complication of coronary ostial stenosis *may* be present, we make a plea for the initiation of antisyphilitic therapy with smaller doses of bismuth than at present advocated.

16. From a practical viewpoint, syphilitic aortitis which is *not arrested* is *progressive*.

17. We believe that the activity of syphilitic aortitis cannot be arrested by the use of heavy metals alone.

18. Therefore, with realization of its inherent dangers, we advocate the employment of arsenoxide (or penicillin, after proper experimentation) in the treatment of every case of syphilitic aortitis in which specific contraindications are not present.

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Seminars on Hypertension

Mechanisms of Human Hypertension*

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AN ELEVATED blood pressure in man should be looked upon as a physical sign reflecting disordered function of the vascular system. It is comparable with jaundice as related to disease of the biliary system and liver. Hypertension may affect the systolic blood pressure alone, the diastolic pressure predominantly or more commonly both. An elevation of the systolic pressure alone with a normal or decreased diastolic pressure is observed in such conditions as aortic insufficiency, arteriovenous fistulas including patent ductus arteriosus, hyperthyroidism, complete heart block and, most commonly of all, atherosclerosis which is such a common accompaniment of advancing age. The systolic hypertension of atherosclerosis is due to a loss of elasticity of the large arteries. Although atherosclerosis can hardly be considered a normal process, its frequency in patients over fifty or sixty is responsible for the lay belief that normal systolic pressure is equal to 100 plus the age.

There is no unanimity regarding the manner by which diastolic blood pressure becomes elevated in man. Some believe that diastolic hypertension is always of primary renal vascular origin. Proof and disproof of this belief is lacking. Although Castleman and Smithwick[1] have been unable to find any significant renal vascular lesions in biopsy specimens in early hypertension, the objection has been raised justifiably that biopsies contain too little tissue to show representative changes in the vessels of the kidney[2,3,4] and that physiologic change may well precede morphologic abnormality.

Many authorities believe that diastolic hypertension is sometimes due to renal disease as in cases of glomerulonephritis, pyelonephritis, the nephrotic syndrome and so forth, but that in most instances it is of extrarenal origin (posterior pituitary, adrenal, central nervous system, unknown factors). Finally, some believe that all diastolic hypertensions in man represent a single entity of diverse etiology and that all are mediated through the kidney whether or not renal disease is apparent. It is believed that not only primary renal disease such as glomerulonephritis but also extrarenal factors may act on the kidney to produce elevation of blood pressure. Thus, pheochromocytomas producing adrenalin give rise in certain instances to a sustained non-paroxysmal type of hypertension indistinguishable from that of benign or malignant essential hypertension.[5,6] Adrenal cortical neoplasms and basophile tumors of the pituitary are usually associated with hypertension. The production of nephrosclerosis and hypertension by the administration of corticoid compounds and sodium chloride to several species of animals by Selye and co-workers[7–14] has been the most direct experimental attempt to relate the adrenal cortex to hypertension and the kidney. Selye's observations have been confirmed[15,16] and denied.[17,18] In man, Perera has shown that the administration of desoxycorticosterone and salt to patients with Addison's disease frequently results in hypertension[19]

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and that their administration to hypertensive patients produces a further rise of blood pressure.[20] Neurosurgeons[21,22] and psychiatrists[23] have suggested that hypertension may be initiated by emotional stress and in time this neurogenic hypertension may produce enough structural change in the renal vasculature to produce hypertension of renal origin. There is no experimental counterpart to this suggestion since neurogenic hypertension in dogs does not produce morphologic changes in the arterioles.[24,25]

Although there is no unanimity of opinion regarding the fundamental mechanism involved in the elevation of diastolic blood pressure in man, the kidney has been the suspected organ for over one hundred years. Such suspicion was greatly fortified in 1934 by the brilliant investigations of Goldblatt and his associates[26] who, for the first time, produced chronic, sustained and readily reproducible hypertension in dogs by partial constriction of the renal artery. Both benign and malignant forms of the disease were produced and these showed striking similarities to the human disease, whereas neurogenic hypertension produced by section of the carotid and aortic sinuses bore little resemblance to human hypertension.[2]

In man there are innumerable factors which at this stage of our knowledge are not controllable, such as race, sex, heredity, aggravation or masking of the true course of the disease by atherosclerosis, diabetes and the like as well as the difficulty of obtaining interpretable blood pressure readings except by the most meticulous measures.[27] At this point little more can be said regarding the nature of human hypertension because developments in this field must await advances in the experimental animal.

An enormous volume of literature has developed in the last decade concerning the mechanism by which the kidney can elevate blood pressure. These studies have been reviewed in detail elsewhere[2] and only the more pertinent reports will be discussed at this time.

The renin mechanism has received the most attention by investigators and although its rôle in the production and maintenance of hypertension is still uncertain, its present status will be reviewed. This mechanism consists of: (1) renin, a globulin produced exclusively by the kidney[2] and is enzymatic in its chemical behavior;[28,29] (2) hypertensinogen (renin activator, renin substrate) which is probably an alpha globulin[30] produced mainly, if not exclusively, by the liver,[31,32] is normally found in easily demonstrable amounts in serum[2] and is the substrate on which renin acts to produce (3) hypertensin (angiotonin), a potent pressor and constrictor substance with a molecular weight[33] of about 2700 and (4) hypertensinase which comprises a group of proteins widely distributed throughout the body even in animals who have none of the other components of the renin system.[34,35] Hypertensinase is enzymatic in nature and destroys hypertensin.[34]

Renin has been identified in the renal venous blood of dogs with renal hypertension[36,37,38] and recently it has been shown[39] that as blood pressure rises following the application of a Goldblatt clamp to the renal artery of dogs, the renin concentration of systemic blood rises but that despite a persistent elevation of the blood pressure, the renin gradually diminishes until it is no longer detectable. Similar amounts of renin have been detected in the blood of some patients with acute hypertension such as acute glomerulonephritis and toxemia of pregnancy.[2,40] In chronic hypertension renin has not been detected in the systemic blood.[2,41] Renin has been found in the renal venous blood of about one-half of a group of hypertensive patients but similar amounts of renin have been found in the renal venous blood in a like proportion of normal individuals.[42] Using an extremely sensitive method of detection, Taquini and Fasciolo[43] have recovered minute amounts of renin from the systemic blood of normal individuals and similar amounts in hypertensive patients. It may be concluded that renin is found in the blood of man and animals during the acute phase of hypertension

but that despite the persistence of an elevated blood pressure, its concentration decreases until it is no longer detectable by current methods of assay.

Although at one time it was reported that in hypertensive dogs and patients the concentration of hypertensinogen in plasma was increased,[44,45] subsequent studies have failed to reveal any significant deviation from normal values.[2,46,47]

The concentration of hypertensinase in plasma has been reported to be decreased in acute renal hypertension in animals[48,49] but this has not been confirmed.[2] In dogs and in patients with chronic hypertension, normal values have been obtained.[50,51] Attempts to identify hypertensin in the blood of hypertensive patients and animals have been unsuccessful.[52,53]

It is seen, therefore, that renin, hypertensinogen and hypertensinase concentrations of plasma are similar in man and in animals in acute and chronic renal hypertension. No consistent abnormality of this system has been found in chronic hypertension although in the acute stages renin has been found to be present in amounts sufficient to account for the observed rise of blood pressure.

Currently there are three possibilities which have been expressed to explain the findings documented above:

1. Renin plays no rôle in the pathogenesis of hypertension of renal origin. Although it has been shown to come into action in peripheral circulatory collapse,[54,55,56] its effectiveness in combatting shock is slight.[57,58]

2. Renin may initiate renal hypertension and some other pressor mechanism may take over the function of its maintenance. Ogden and co-workers[59–63] have suggested this as a possibility. They have reported that the sympatholytic agents, yohimbine and F883, produce no fall of blood pressure in animals with early hypertension while in chronic hypertension these drugs produce a fall of blood pressure. On this evidence Ogden and his associates have suggested that the sympathetic nervous system is somehow responsible for the maintenance of sustained hypertension. It is well known, however, that complete sympathectomy both in animals [64–66] and in man[67] fails to cure long-standing hypertension. It would be of interest to know whether the presence of renin in early hypertension determines the difference in the behavior of these sympatholytic drugs. It has been suggested by Grollman and co-workers[68] that chronic stages of hypertension are due to a lack of some substance essential for the maintenance of normal blood pressure. They note that the blood pressure of hypertensive rats falls during pregnancy which Page[69] has recently attributed to an increase in the concentration of plasma hypertensinase in pregnant women. Grollman and co-workers have also reported a greater sensitivity to renin of pregnant than of non-pregnant rats, that unilateral nephrectomy in the rat and rabbit produces in some cases a rise of blood pressure[70,71] that bilateral nephrectomy in hypertensive rats does not cause the blood pressure to drop to normal levels and that bilateral nephrectomy in normal rats produces a slight rise of blood pressure.[70] Other investigators, however, have reported that after bilateral nephrectomy in dogs the blood pressure, if elevated, falls to normal[72–74] and if normal, does not rise.[73,75–79]

3. During the acute phase of hypertension renin may be present in the blood in excessive, easily measurable amounts and during the chronic stage of hypertension the amount of renin necessary to maintain hypertension may be too small to detect by current methods of bio-assay. Wakerlin and Goldblatt have made interesting and pertinent observations in this regard. Abandoning the relatively insensitive methods of bio-assay for renin, Wakerlin and his collaborators[80] made the important observation that injection of hog renin into a dog produced an antibody (antirenin) not only to the hog renin but also the dog's own renin. They first reported that the blood pressure of hypertensive dogs fell as the antirenin titer became elevated. Subsequently, they observed that an elevated

antirenin titer in the blood did not prevent the development of renal hypertension nor did it necessarily effect a fall of blood pressure in hypertensive dogs. On the other hand, a fall of blood pressure sometimes occurred in hypertensive animals without a significant rise of antirenin titer.[81,82]

Goldblatt[83,84] reports that using a more highly purified hog renin and possibly obtaining somewhat higher antirenin titers than Wakerlin, a high antirenin titer not only prevented hypertension by constriction of the renal artery but consistently caused the blood pressure of dogs made hypertensive months or years before to return to entirely normal levels.

There the matter stands at the time of this writing. If a high antirenin titer invariably causes an elevated blood pressure to return to normal, attempts should be made to produce an antibody against human renin, which so far have been unsuccessful. If hypertension can exist in the face of a high antirenin titer, renin is obviously not the cause of renal hypertension and the pathway of future investigations might well follow the leads suggested several years ago by Bing[85–87] or be directed toward the VEM as described by Shorr and co-workers[88–90] in this series of articles.

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Combined Staff Clinics

Hepatitis

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. FRANKLIN M. HANGER: Since this country entered the last World War it has been estimated that over a million Americans have become victims of acute hepatitis. This disease has been so prevalent on our wards that there are probably few of you who do not believe that you are experts in the diagnosis of liver disorders. Therefore, we will not deal with the various clinical manifestations of hepatitis but will stress certain aspects of the subject which are still not well understood and still controversial.

It might be profitable to review briefly with you the changes that occur in the liver during hepatitis. Recent biopsy studies made by a number of observers during the preclinical stage of the disease as well as during the period of jaundice and convalescence have revealed that the lesions do not consist solely of parenchymal destruction, as was formerly believed, but that other structures of the liver are commonly involved. Mallory, in an excellent histologic report of a large number of cases of hepatitis studied in volunteers,* has pointed out that the chief portions of the lobule affected are (1) the polygonal cells forming the liver cords, (2) the reticuloendothelial lining of the sinusoids and (3) the portal and periportal areas at the periphery of the lobules. In most cases of hepatitis all three of these types of lesions are present, involvement of the parenchymal cells, the Kupffer cells and the periportal areas.

Figure 1 is a diagram of the normal human liver which shows in a schematic way where the virus of hepatitis strikes. First, the cords of the parenchyma become distorted and swollen. The affected cells become eosinophilic, lose their normal granulation and appear as homogeneous red-staining material in which the nucleus becomes fragmented and pyknotic. Later these cells gradually disappear. The extent of the lesions in different cases varies from only a few scattered abnormal cells to entire destruction of the lobule. As parenchymal involvement increases, a corresponding impairment of the various functions of the liver may be demonstrated by standard tests.

The second type of lesion involves the sinusoids. The Kupffer cells which line the spaces through which blood flows between the liver cords are swollen. They become highly proliferative and sometimes the sinusoids are actually blocked by a great number of histiocytes which are assumed to be the result of multiplication of the Kupffer cells. Disturbances of the reticuloendothelial elements may lead to portal hypertension, impairment of the removal of certain substances of the blood and to the elaboration of abnormal serum globulins.

Third, and equally important, are the inflammatory changes in the portal and periportal areas. These portions of the liver become infiltrated chiefly with histiocytes, lymphocytes, a few polymorphonuclears and eosinophiles, with considerable congestion and swelling of the interstitial tissues.

An understanding of the morphologic changes occurring in hepatitis is essential to an understanding of the differences all of you have noticed in the laboratory findings

* MALLORY, T. B. The pathology of epidemic hepatitis. *J. A. M. A.*, 134: 655, 1947.

in individual cases. In rare individual cases we find one element involved almost exclusively, and liver biopsies of such cases give us an explanation of why liver functions may vary in the different types of hepatitis. For instance, when the Kupffer cells become swollen and inadequate, laboratory studies show a negative cephalin flocculation test, the serum alkaline phosphatase is somewhat elevated and there is an increase in the indirect or delayed-reacting bilirubin of the serum. The metabolic functions of the liver cells, as indicated by cholesterol ester levels, galactose tolerance tests, etc., are relatively unimpaired. There may be enlargement of the spleen, ascites and evidence of portal congestion.

When the parenchymal cells are chiefly involved, the cephalin flocculation and thymol turbidity tests are positive but the phosphatase is not significantly elevated. The direct, prompt-reacting bilirubin of the blood tends to be elevated, and various metabolic functions as indicated by cholesterol esters and galactose tolerance show impairment.

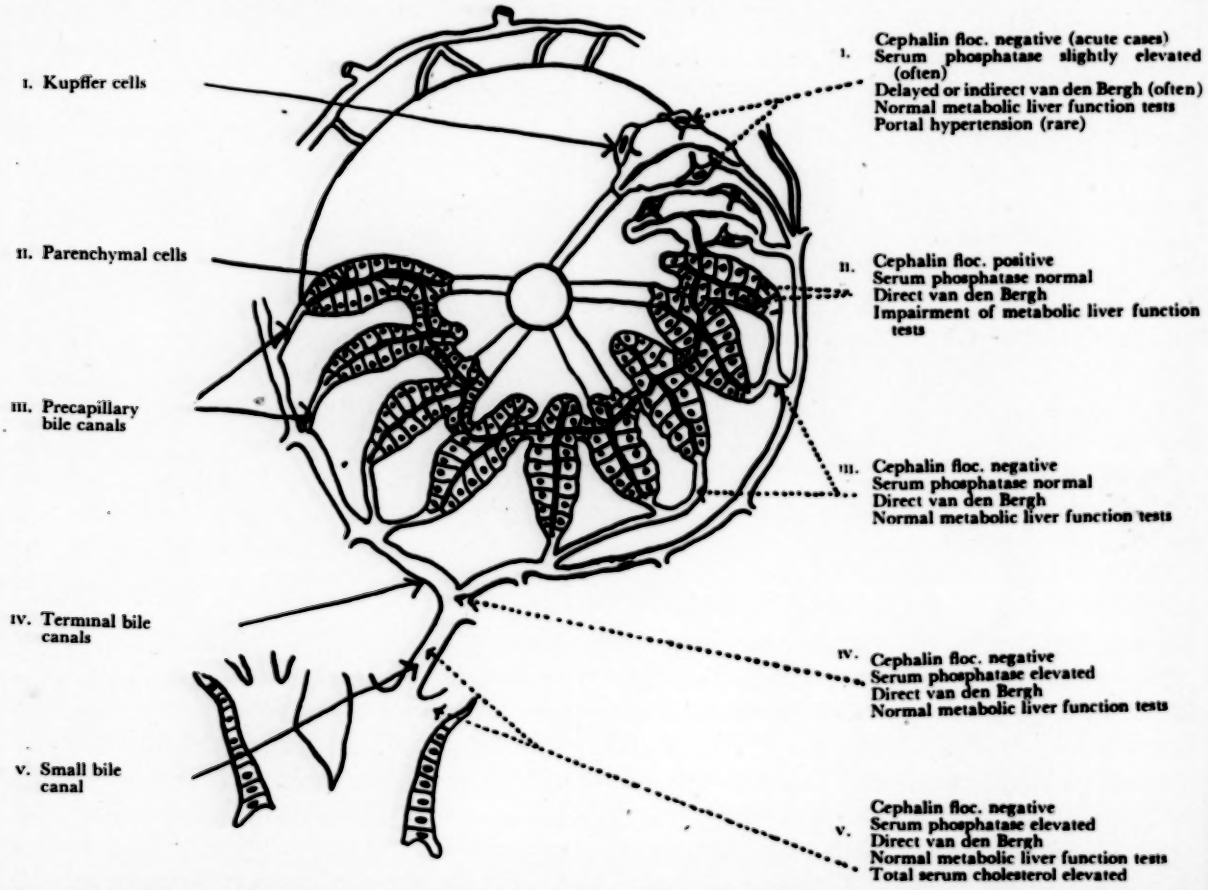
I. Kupffer cells
II. Parenchymal cells
III. Precapillary bile canals
IV. Terminal bile canals
V. Small bile canal
I. Cephalin floc. negative (acute cases)
Serum phosphatase slightly elevated (often)
Delayed or indirect van den Bergh (often)
Normal metabolic liver function tests
Portal hypertension (rare)
II. Cephalin floc. positive
Serum phosphatase normal
Direct van den Bergh
Impairment of metabolic liver function tests
III. Cephalin floc. negative
Serum phosphatase normal
Direct van den Bergh
Normal metabolic liver function tests
IV. Cephalin floc. negative
Serum phosphatase elevated
Direct van den Bergh
Normal metabolic liver function tests
V. Cephalin floc. negative
Serum phosphatase elevated
Direct van den Bergh
Normal metabolic liver function tests
Total serum cholesterol elevated

FIG. 1. Diagram of an hepatic unit representing an attempt to correlate the location of the lesion in hepatitis with changes in the laboratory findings. It should be emphasized that the relationships indicated are tentative only since the available data upon which the schema is based are inadequate. Adapted from Lichtman, "Diseases of the Liver." (Redrawn from L. Aschoff. *Verhandl. d. deutsch. Gesellsch f. inn. Med.*).

In rare instances of hepatitis the patient is deeply jaundiced and yet the cephalin flocculation test is negative and liver function tests are normal. We have had biopsy studies in three of such patients and in all an intense inflammatory zone surrounding the lobule was the sole lesion. The liver parenchyma appeared normal and the Kupffer cells were not particularly prominent, but areas of free bile accumulating like little puddles could be seen in the inflamed perilobular zone as if there were disruption of small bile canaliculae with extravasation of bile into the tissues.

Patients with this lesion, as I said, give us very little evidence of liver impairment by ordinary tests. The striking feature is a deeply jaundiced person, feeling quite well and with normal liver function tests.

When the portal areas become involved there is more injury to the liver, directly and indirectly, than one would suppose at first glance. It is through this area that the portal blood passes into the lobule and lymphatic drainage takes place. It is also through this area that the smaller bile ducts pass. When the periportal areas become swollen and congested there is frequently pressure on all structures traversing them. Just as injuring the stem may affect the development and quality of a cluster of grapes, so may inflammatory processes in the portal area affect the blood supply and functioning of the hepatic units.

STUDENT: Dr. Hanger, do not these variations in the pattern of liver involvement in hepatitis make it very difficult to establish the diagnosis of hepatitis by laboratory tests?

DR. HANGER: Fortunately from the standpoint of the clinician, cases of hepatitis rarely fail to show some indication of parenchymal damage. Hepatitis of the cholangitic type in patients over forty is particularly disturbing when the laboratory findings point strongly to the jaundice being of the obstructive type. In such instances the disorder should be followed for at least six weeks; if there is no improvement, abdominal exploration is indicated to rule out stone or neoplasm. An operation in such cases is not entirely futile, even when extrahepatic obstruction is not found; for clearing of the jaundice sometimes follows exploration and drainage of the common duct in instances of cholangitis with intrahepatic obstruction. The reason for the beneficial effect of this procedure is not clear.

We must go on now to the question of the etiology of hepatitis. Dr. Neefe, of the University of Pennsylvania, an investigator who has contributed a great deal to our understanding of the agents causing the disease, is with us this morning and we have asked him to tell us about his work.

DR. JOHN R. NEEFE: It might be well to review rather briefly the known facts about the etiology of this disease or perhaps we should say family of diseases.

I would like to emphasize that many of the comments that I shall make today are the result of the pooled observations of many workers and, while some of the observations refer to work done at the University of Pennsylvania in conjunction with Dr. Joseph Stokes, Jr., Dr. John Reinhold, Dr. Sydney Gellis and others, they often were preceded, obtained independently, or else confirmed by the observations of other workers, including Havens, Paul, Oliphant, Cameron, Voegt, MacCallum, Findlay, and a number of other workers in England.

The etiologic agents involved in the problem of viral hepatitis have many properties which justify their tentative classification as viruses even though, as you all know, they have not been isolated or visualized and the evidence, therefore, is indirect. From the literature, one can garner quite a number of observations which give us some idea about these properties, and while they may not hold for all the strains of virus concerned—actually we do not know how many are involved—they do illustrate their probable general characteristics. We know that the etiologic agent of viral hepatitis passes through bacteria-retaining filters. We know it survives heating for at least an hour at 56°C. More recently, however, it has been shown that at least one of these strains of virus is inactivated, under certain conditions, by heating at 60°C. for a period of ten hours. This was under special experimental conditions and whether a shorter period of heating or a lower temperature would have been adequate is not yet known. However, there is this evidence that the virus can be destroyed by heating and fortunately such treatment can be applied to certain preparations, such as human serum albumin, which are now coming into more widespread use. Un-

fortunately, this treatment cannot be applied to whole blood, plasma or serum because, apparently, denaturation or coagulation of other proteins occurs. Oliphant has obtained some evidence to suggest that the viruses in plasma may be inactivated by exposure of the plasma to ultraviolet light. These data are not conclusive and as yet we do not know whether this affords a practical and effective means of treatment of blood products that is adaptable to large scale application.

We know that this virus (or group of viruses) survives for long periods under rather diverse conditions: tropical conditions, arctic conditions, and for long periods of time in our laboratories at room temperature. They survive in the presence of concentrations of certain disinfectants which apparently are adequate to control bacteria, for example, merthiolate, equal parts of phenol and ether, and others. These observations are important because they indicate the sturdiness of these agents and account for many of the problems that arise in their control.

No consistent or reproducible lesions have been observed in chick embryos that have been inoculated with infectious material and definite evidence of propagation of these viruses in tissue culture has not been obtained. No inclusion bodies have been found in the pathologic studies on material from patients with hepatitis. The most serious problem, from the viewpoint of investigation, has been the failure to find a susceptible laboratory animal, which, as you all know, is the reason why the use of human volunteers has been necessary for most of the studies to date.

We were fortunate during the early stages of our work to obtain materials that appeared to contain viruses that apparently caused somewhat different types of hepatitis under somewhat different conditions. It now seems that these two strains of viruses, the exact relationship between which is not known, are responsible for the two similar forms of hepatitis that we now recognize clinically, namely, so-called *infectious or epidemic hepatitis* and so-called *homologous serum hepatitis*. For convenience in reference, we have called the one strain, obtained from persons with infectious hepatitis, *Virus IH*, and the other has been referred to as *Virus SH*. The behavior of these two strains of virus in human volunteers differed consistently. For example, there was a rather characteristic difference in respect to the type of onset of the disease in these experimental cases. However, from the literature and clinical observations it appears that the more abrupt onset and the more frequent occurrence of fever of significant degree with the onset of infectious (virus IH) hepatitis, as observed in the experimental cases, are not sufficiently consistent to serve as a means of differentiation between the two types of hepatitis. Yet experimentally it was a rather consistent difference.

Also consistent was the difference in interval from inoculation to the onset of hepatitis and this was true regardless of the route of entry of the virus. Thus, regardless of whether virus IH was given orally or parenterally, the incubation period was the same, that is, between eighteen and thirty-seven days. However, when virus SH was injected parenterally, a period of two to five months consistently elapsed before the onset of the recognizable disease. It was of interest that when this virus (SH) was given parenterally, the incidence of hepatitis in volunteers was very high, approximately 75 per cent. However, when it was given orally, neither in our series nor in that of Dr. Havens at New Haven did recognizable hepatitis result. When virus IH was given orally, the incidence of virus hepatitis was very high, approximately 80 per cent. In Dr. Havens' volunteers, the incidence with this type of virus (IH) was about the same regardless of whether it was given orally or parenterally. With our strain of virus IH the incidence in normal volunteers after parenteral injection was rather low but it was capable of inducing the disease by this route. These observations demonstrate a point that I desire to emphasize, namely,

that homologous serum hepatitis actually is not a single etiologic entity. It is a syndrome that may be the result of either one of these two strains of virus and therefore we must recognize at least two syndromes when we face clinically the problem of so-called homologous serum hepatitis. In the one the onset occurs two to six weeks after entry of the virus (IH), and with the other the onset occurs two to six months after entry (virus SH type).

Another interesting difference experimentally is the fact that virus IH usually is present in the feces of patients during the active disease. I might point out at this time that it is not yet known how long the virus persists in the feces and therefore it is not possible to give an accurate estimate as to how long it is necessary to maintain infectious precautions. Interestingly, it has not yet been possible to demonstrate virus SH in the feces of patients with this disease. However, these experiments are incomplete in that most of the virus SH preparations were administered orally. As plasma known to contain virus SH and to produce the disease when given parenterally has failed to induce recognizable hepatitis when given orally, the absence of positive disease on oral administration does not conclusively show that feces do not contain the virus. This may only mean that this virus is not very effective when it enters by any route other than the parenteral one.

The studies on immunity were perhaps most significant in demonstrating the existence of an actual difference, at least antigenically, between these two strains of virus. Volunteers who had virus SH hepatitis and after recovery were reinoculated with the same strain of virus were resistant to reinfection up to at least one year, the longest period of time after which the presence of homologous immunity was tested in our series. However, these same volunteers who were resistant to reinfection with virus SH were not resistant to virus IH, developing the typical disease when inoculated with this virus. The experiment could be reversed and run in the opposite direction; volunteers who had had virus IH hepatitis and had been shown to be resistant to reinfection with this virus developed typical disease two to four and one-half months after inoculation with virus SH.

It is interesting that during the two- to four-month interval between inoculation with virus SH and the onset of the recognizable acute hepatitis some of the volunteers had several periods of transient minor symptoms. These were not very significant clinically, consisting merely of a day or so of malaise and mild symptoms. In some these periods were associated with slightly abnormal results of certain hepatic tests. Of great importance is the fact that blood taken from such volunteers during these (and even completely asymptomatic) periods has been shown to contain the virus. These observations suggest that, although there is this long interval, there may be some activity of the disease during the long interval. The occurrence of viremia in the absence of significant clinical symptoms and before the onset of acute hepatitis is one of the serious problems contributing to the difficulties in control of the disease and indicates the probable relative ineffectiveness of exclusion of blood donors with a history of overt hepatitis as an adequate means of prevention.

I think then, on the basis of the evidence available, we can say that the existence of at least two somewhat different strains of hepatitis viruses has been adequately demonstrated and, although the possibility of existence of other strains remains, our approach to the viral hepatitis problem, for the time being, has to be centered about the existing knowledge concerning the two recognized strains.

I think it is fairly obvious from the discussion thus far that, experimentally at least, there is evidence of homologous immunity following an infection with either of these viruses but that effective cross immunity does not occur. These experimental data are supported by clinical and epidemiologic observations. Thus it was observed during the war by Dr. Gauld and

others that persons who had so-called yellow fever vaccine or post-vaccine hepatitis were, if anything, more susceptible at a later date to epidemic hepatitis than were those who had not had the post-vaccinal disease. Likewise, persons who had had "catarrhal jaundice" or sporadic hepatitis prior to military service developed post-vaccinal hepatitis with the same frequency as those who had not.

With respect to the question of second attacks, we have all seen patients who tell us that they have had hepatitis or jaundice two or three times, separated by long asymptomatic intervals. It often has seemed reasonable to assume that these represented second attacks of the same disease. A history of two attacks of hepatitis is obtained in approximately 2 to 5 per cent of patients with jaundice. However, in view of what we now know, we cannot assume that these second attacks necessarily were due to the same virus or that they necessarily constitute evidence against the existence of prolonged homologous immunity following an attack of virual hepatitis. For example, I recently have seen a patient who had virus IH hepatitis in 1944 and in 1947 a second attack of jaundice that clearly was associated with infectious mononucleosis.

Some interesting theoretical possibilities in regard to immunity are suggested by the studies on gamma globulin as used in attempts to protect passively against these two diseases. I think it is fair to say at the present time that most of the workers in this field accept the evidence that gamma globulin is an effective prophylactic agent against the epidemic or virus IH type of hepatitis. If it is given to exposed persons during the incubation period prior to the onset of symptoms, a very marked decrease in the incidence of the disease in those receiving gamma globulin has been noted under epidemic conditions.

In relation to serum hepatitis the results with gamma globulin have been confusing and difficult to interpret. Experimentally, when plasma containing virus SH was mixed with gamma globulin, as in a neutralization test, and the mixture injected into volunteers, the incidence of the disease was not reduced nor was the course of the disease obviously modified. Thus the gamma globulin used either did not contain protective substances effective against virus SH under the conditions of the experiment, or if present, they were not present in sufficient concentration to protect. Likewise, when virus SH was injected parenterally at the same time gamma globulin was injected at a different site, the incidence of hepatitis was the same as in the group of volunteers who received only virus SH.

There are some data on this point from studies in Army hospitals where battle casualties who had been given transfusions later received gamma globulin. There were two such studies. In one study by Duncan and his associates, battle casualties received one dose of gamma globulin on admission to an army general hospital. The patients all had a history of blood or plasma transfusions during the preceding several months. No effect on the incidence of serum hepatitis was detected in this group. However, in another similar study by Grossman, Stewart and Stokes, two doses of globulin were given at intervals of one month. In this series, the data indicated a decrease in incidence as compared with that in battle casualties who had been given transfusions and who did not receive gamma globulin. These observations, however, plus the experimental data cited, indicate that gamma globulin has not yet been proved conclusively to be an effective means of prophylaxis against serum hepatitis (virus SH type) and I think sufficient work has been done to say that it does not seem to afford the same protective effect against the virus SH type of hepatitis that it does against the epidemic virus IH type.

This suggests several theoretic possibilities concerning the extent of the natural distribution of these two types of hepatitis virus. Gamma globulin is prepared from large pools of human adult plasma. If we assume, on the basis of the studies mentioned, that there is a reasonable quantity

of "protective substances" in gamma globulin effective against virus IH, it seems fair to assume that many adults have been exposed to this disease at some time in their lives. On the same basis, it seems possible that relatively few persons, at least prior to the introduction of the large scale use of blood and its products, had been exposed to the SH type virus. This seems reasonable in view of our present knowledge concerning the two viruses, namely, the fact that virus SH does not seem to be very effective in inducing overt hepatitis when it enters by any other route than by the parenteral route. These various observations suggest that the IH strain of virus may have been much more widely distributed in the general population than was the virus SH strain. It is interesting then, if this is the case, that most of the large hepatitis outbreaks resulting from injections of blood or its products, or of biologicals containing blood products, have been of the virus SH type. One would expect, on the basis of the suggested frequency of distribution, that the virus IH type of hepatitis in relation to transmission by blood or its products would be more frequent than the virus SH type. It seems to me that this possibly could be explained by the inclusion in large plasma pools of sufficient "protective substance" from the plasma of immune adults to neutralize any IH type virus that also might be included; whereas, if few adults have "protective substances" effective against virus SH, any virus of this type that is present would not be neutralized. I wish to emphasize that this is purely a theoretical explanation and that there is no factual basis for it as yet except that it does seem to be in accord with some of the known indirect facts. If true, we possibly should expect to find most of the cases of serum hepatitis due to virus IH (short incubation period) occurring in relation to the use of whole blood.

It seems important, therefore, to get away from the concept of the syndrome of homologous serum hepatitis as a single etiologic type, namely, the long interval (virus SH) type. The syndrome actually is composed of at least two forms of hepatitis, one (virus IH type) occurring two to six weeks after injection of a blood product and the classical (virus SH) type occurring after two to six months.

What are the various ways in which such viruses can be acquired? When one considers the many opportunities for entry of a virus by the parenteral route inherent in modern methods of medical practice, the extent of the problems created by the changes that appear necessary for prevention becomes alarming. Opportunities for viral entry obviously exist with every injection of blood, plasma or serum, and with injections of biologic products containing plasma or serum. The outstanding example of the latter is the U. S. Army outbreak in 1942 associated with the prophylactic injections of yellow fever vaccine. As you know, the yellow fever vaccine contained a small amount of serum which apparently was responsible for hepatitis virus transmission to tens of thousands of army personnel. Over 50,000 cases are thought to have been infected from this source.

More recently attention has been directed toward the possible transfer of these viruses by means other than intentional injection, namely, by the use of improperly sterilized syringes and needles. This is made possible by the resistance of the viruses to commonly used disinfectants and by the small quantity of serum (.01 cc. or less) required for transmission of the virus. The evidence of hepatitis virus transfer by this method is again indirect but nevertheless it is good enough to oblige us to face the reality until proved otherwise.

How does this occur? First of all, it is obvious that in attempting to withdraw blood from a vein with a syringe we may create considerable suction by pulling strongly on the plunger in an effort to obtain blood more rapidly. This often collapses the vein and the negative pressure very readily sets up conditions where there could be reflux back and forth between the vein and the syringe. Further, there is

evidence from England to show that when the tourniquet is released a momentary negative pressure in the vein is produced which is sufficient to withdraw a small quantity of blood from the needle.

In the procedure of using syringes and needles simply for injections it is common practice in immunization or therapeutic procedures applied on a mass basis to use the "single syringe-multiple dose technic" and simply to change the needle or perhaps just wipe the needle between patients. As many of us have been taught always to aspirate before injecting, it is quite possible in using this "single syringe-multiple dose technic" to contaminate the syringe contents with hepatitis virus from one person and then infect a group of persons with the multiple doses from the remainder of the contents.

Attention has been drawn to the possibility of transfer of hepatitis virus even by the finger puncture technic commonly used in doing blood counts. Ordinarily, the stylet or needle used for puncturing the finger is just washed off or immersed in alcohol and then is used on the next person.

Finally, it has been suggested that transfer may sometimes occur from syringes or needles used for injecting procaine, by dentists for example. There are so many potential sources that the problem becomes extremely difficult.

In Germany this summer, Dr. Havens and I had the opportunity to see approximately 300 cases of hepatitis in the U. S. Army Hepatitis Center. Of interest was the fact that nearly all of these patients had been exposed to some sort of parenteral procedure during the preceding six months.

I would like to conclude my discussion with a few words about infectious hepatitis and its modes of transmission. To date we know only that during the active disease the virus (IH type) may be present in the blood and feces. The problems relating to control in blood are the same as those discussed in relation to the serum hepatitis syndrome. The problems of transmission from feces involve all the possible direct and indirect ways of transmission by contaminated water, food, milk, fomites, direct contact, mechanical transfer by flies, etc. This obviously puts the transmission of this disease and the problems of its control into the same category as some of the other enteric bacterial infections, with the added problem that the hepatitis viruses apparently are more resistant to procedures which ordinarily control bacterial agents.

There are a number of other aspects of hepatitis that are worthy of discussion but I have taken about all of my time and perhaps these other aspects will arise during the open discussion.

STUDENT: Has the recent extensive pathologic study of this disease brought out anything that would help to tell one type of hepatitis virus infection from the other by their histologic characteristics?

DR. NEEFE: I think that pathologists like Lucké and Mallory, who have done much of the recent work in this field, are agreed that they cannot distinguish what presumably is a case of virus SH hepatitis from virus IH hepatitis.

I might point out one interesting observation for what it is worth. How consistent or significant it is I do not know. Dr. Reinhold and I have been interested in the results of the various hepatic tests in these two types of hepatitis (IH and SH) and there does seem to be a difference in the response of the thymol and colloidal gold tests in the virus SH group as compared with the virus IH group. In a number of those who had virus SH hepatitis the thymol test either failed to become abnormal or became only weakly positive, whereas in the experimental virus IH hepatitis group the thymol and colloidal gold responses consistently were markedly abnormal. These trends were quite consistent in the experimental groups and while I do not think one can depend on them to differentiate the two diseases, because of individual exceptions, the observations have some clinical significance in the fact that a positive thymol test is not essential for the diagnosis of viral hepatitis. Some of the published results

had led us to expect that the thymol turbidity test would be positive during acute hepatitis but our own observations indicate that one should not necessarily expect a positive thymol test, particularly in virus SH hepatitis. The cephalin flocculation test was consistently positive in both groups, except for one case of virus SH hepatitis in which none of the "flocculation" tests became positive during the entire course of the disease.

DOCTOR: Is the sum total of your studies, Dr. Neefe, plus those of Dr. Havens and others, adequate to say whether or not there is any consistent difference in duration of course in the prognosis of the two diseases?

DR. NEEFE: I think the actual duration of the course cannot be considered significantly different in the experimental groups. When one considers the various series reported in the literature, it is a different story and it does seem that the prehepatitis condition of the persons involved is an important factor. This is a clinical problem which we face in civilian life in respect to serum hepatitis. Often occurring in older people, in persons who have been in a hospital for some other illness or who have had serious operations, the nutritional status frequently is poor before the onset of hepatitis and, moreover, other diseases may coexist. In battle casualties the same situation occurred. One group reported by Dr. Snell and others had an estimated mortality rate of 19 per cent. Yet, in the 1942 yellow fever vaccine outbreak, which involved army personnel who were healthy, well nourished and in good physical condition, the mortality and the morbidity, as far as we can tell, did not differ much from that observed in the epidemic or virus IH type under similar conditions.

DR. HANGER: Dr. Neefe, I would like to ask a question which I am sure is in the mind of many in the audience. I would like to know how you at the University of Pennsylvania Hospital segregate your cases of acute hepatitis, what precautions you institute and when you relinquish these precautions.

DR. NEEFE: I might say at the start that it is hardly possible to take all the precautions that seem indicated on the basis of our present knowledge. Our principal objective is to do all that can be done in a hospital to prevent transmission from feces and from blood. Patients are put on what might be called "intestinal isolation" in the same fashion as are typhoid patients. This is maintained until discharge from the hospital. As no one knows how long the virus persists in feces, the length of time such precautions should be maintained is purely a guess. We usually suggest that special care be taken until at least two weeks after jaundice disappears. Fortunately, the duration of hospitalization in the average case is not so long that continuation of "intestinal isolation" for the entire period becomes impractical.

Efforts to prevent transmission from blood should be directed toward diminishing the opportunities by which this may occur. This requires, among other obvious precautions, special attention to venous and finger puncture technics and to the whole question of the handling of syringes and needles. This matter was recently laid before the Subcommittee on Liver Diseases of the National Research Council by means of a formal direct request from one of the federal agencies for advice as to what procedures should be instituted regarding the routine handling of syringes and needles. The opinion of the Subcommittee was unanimous that all syringes and needles be properly cleaned and sterilized by heat before use in each patient. This presents a real technical problem for large hospital services and I do not know how it can be done in a simple way. It probably is the only certain way of eliminating the risk entirely. How great the risk is if one does not take these precautions is hard to define. However, as the evidence does indicate that failure to observe such precautions involves some risk, it is our obligation to recognize and eliminate the sources of risk insofar as possible. One way of simplifying the syringe problem to some extent is to eliminate the

use of a syringe for drawing blood specimens whenever possible. The use of a needle and a short piece of rubber tubing often suffices for collection of blood specimens, particularly small ones. The use of the "multiple dose—single syringe technic" for mass therapeutic or immunization procedures, although convenient, is to be condemned.

Although urine has not been proved to be a definite source of hepatitis virus, it seems wise to take the same precautions in handling specimens from hepatitis patients as are used in the management of typhoid cases.

There appears to be no conclusive evidence of nasopharyngeal droplet transmission of hepatitis virus during the active stages of the disease although such transmission, particularly during the incubation period, has not been excluded. At the present time, therefore, there seems to be no definite indication of any need for special measures, other than reasonable care, directed toward the prevention of droplet transmission from hospitalized patients during the *active* disease.

DR. HANGER: It is obvious that no uniform or satisfactory procedure is being followed in our general hospitals. I have recently written to the directors of a number of our leading medical clinics asking what routine has been inaugurated in their institutions to prevent the spread of hepatitis by contact and by venipuncture. The precautions enforced at all these places seem to be tempered with optimism and wishful thinking. In none, however, has a major outbreak of hepatitis been observed among patients or hospital personnel. It would, therefore, seem that a reasonable ward routine and the use of clean, dry syringes are quite effective in curbing the spread of this disease.

DR. ALBERT W. GROKOEST: How soon after your patient with hepatitis is discharged do you use his bed?

DR. NEEFE: I think that the famous remark of Dr. Rivers is apropos, namely, that all of humanity is covered with a thin layer of human feces. Thus it appears that the complete elimination of all sources of contact with virus in a hospital would require superhuman measures beyond the realm of possibility at the present time. Disinfection of the bed linen and blankets, of course, is easily accomplished. Bedside and other utensils can be disinfected with relative ease. The bed mattress is more difficult and whether it is sufficiently important to require some special means of disinfection is unknown. In other words, it does not seem practical at the present time to delay for long the re-use of hospital beds.

DR. HANGER: We might turn now to a consideration of the more chronic forms of hepatitis and their management. I know of no series of cases that have been better studied than those involving Navy personnel observed at the Rockefeller Hospital during the war. Dr. Kunkel, with his associates Dr. Labby and Dr. Hoagland, were able to follow the course of the disease with a wide variety of tests by which the therapeutic value of diet and various medications could be appraised. They have also noted the criteria by which the transition from acute hepatitis to the chronic form can be recognized. Dr. Kunkel will talk to us on these two important aspects of hepatitis.

DR. HENRY G. KUNKEL: For a proper discussion of the treatment of infectious hepatitis and its sequelae it is necessary to consider in some detail the types of chronic liver disease that may develop after an attack of infectious hepatitis. This problem is of particular importance at the present time because the chronic complications of the many cases which occurred during World War II are now beginning to become evident.

The experience derived from a follow-up study of 400 Navy men with acute infectious hepatitis who were admitted to the Rockefeller Hospital during 1944 and 1945 permits certain conclusions to be drawn regarding the chronic aspects of the disease. The most common complication observed in this group was a relapse during convalescence which occurred in 15 per cent of the patients. This was readily detected by a rise in

bromsulfalein retention and in values for the thymol turbidity test. During normal convalescence the bromsulfalein retention falls to normal along with the bilirubin level. The thymol turbidity of the serum falls somewhat more slowly. In the patients suffering relapse the bromsulfalein retention suddenly rose again and remained elevated for from two weeks to three months. The thymol turbidity of the serum also rose but much more slowly and remained abnormal for as long as six months. The bilirubin level of the serum remained normal throughout the period of relapse except in the very severe cases. Associated with these changes in liver function was a return of mild symptoms of liver tenderness, anorexia and fatigue. In almost every case the relapse followed the period when the men were first returned to full activity. It appeared as if the liver were unusually sensitive to further damage through exercise during this period.

As soon as a relapse was detected, the men were returned to bed until values for bromsulfalein retention returned to normal. All but two of the patients suffering relapses recovered uneventfully. These two showed slight persistent signs of liver insufficiency along with intermittent bromsulfalein retention for more than eighteen months after the period of relapse.

A second group of four patients never showed significant improvement following the initial attack of infectious hepatitis and developed a severe chronic hepatitis. At the present time, two years after the initial attack, they still show marked fatigue on exertion, episodes of liver tenderness and marked bromsulfalein retention. These patients appear to have early cirrhosis of the liver.

A third group of seven patients showed a persistent selective abnormality in bilirubin metabolism although all other liver function studies were normal. The bilirubin level of the plasma remained slightly elevated for more than one year after the initial attack. Three of the seven patients continued to have symptoms of fatigue along with bilirubin elevation.

The patients that have been discussed thus far were those who showed a divergence from normal convalescence. The remainder of the 400 patients were discharged free of symptoms and with normal liver function tests after the initial attack of infectious hepatitis. However, follow-up studies have indicated that approximately 60 per cent of this group have shown symptoms attributable to liver dysfunction at some time during the past two years. The symptoms in order of frequency are as follows: undue fatigue, drowsiness, intolerance to alcohol, liver tenderness and intolerance to fatty foods. Liver function tests carried out in these individuals have shown very little impairment. They are all gradually recovering completely and the possibility of serious complications in this large group appears remote.

None of the group of 400 patients who have been followed from the onset of the initial attack of infectious hepatitis has developed ascites or other evidence of severe cirrhosis. However, the fact that a severe and sometimes fatal cirrhosis may develop following infectious hepatitis is clear from studies carried out in four other young service men who incurred their initial attack under wartime conditions. Laparotomy biopsy or autopsy material was available in each case. The gross appearance of the liver was unusual in all of the four patients, being characterized by an irregular nodularity. Large nodules 1 to 2 inches in diameter were prominent. Sections of the liver showed that these nodules were large masses of regenerated liver cells without a lobular pattern. Surrounding these nodules were dense areas of fibrous tissue without any liver cells. The picture was different from the usual Laennec's cirrhosis and most closely resembled the post-necrotic type of cirrhosis originally described by Mallory.

With this brief introduction to the chronic complications that may ensue following infectious hepatitis, we might go on to consider the therapy of this disease during the acute and chronic stages. Two main types of therapy have been proved to be of value during the acute stage: (1) bed rest; (2)

dietary regulation. The value of prolonged bed rest was clearly established by numerous army groups who investigated the disease, as well as by our own study. The time necessary for liver function tests to fall to normal following the institution of bed rest therapy

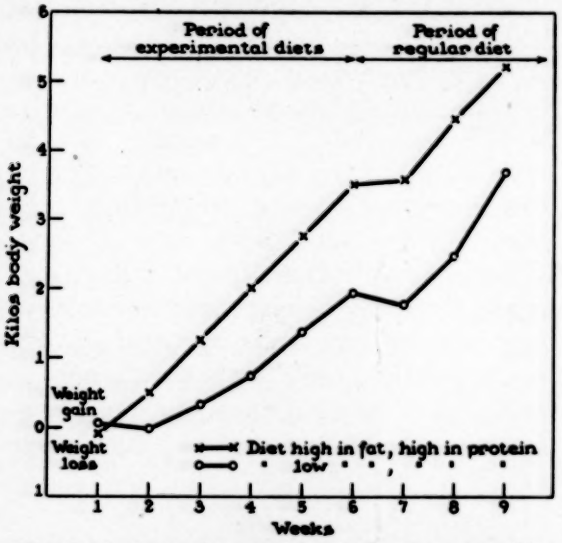

FIG. 2. A comparison between the average weekly increase in weight in a group of thirty-seven patients with infectious hepatitis on a diet high in protein and high in fat and that in thirty-three patients on a diet high in protein and low in fat.

was approximately the same regardless of how long after the onset of the illness the patients were started on this therapy. The development of relapses following the first period of activity attested further to the value of bed rest during the acute stage of the disease. Our patients were kept in bed as long as any impairment in bromsulfalein excretion was present.

Tne second point, dietary therapy, has been the subject of much dispute. When we began our program the dictum against the inclusion of fat in the diet of patients with acute liver disease was firmly established. However, controlled studies on the effect of a high fat diet versus a low fat diet in patients with infectious hepatitis demonstrated that the high fat group improved more rapidly than the low fat group. Figure 2 illustrates the more rapid weight gain in the high fat group. The time necessary for the bromsulfalein retention to return to normal was slightly shorter in the high fat group. These studies indicate that strict limitation of fat in the diet actually has some harmful effects. The anorexic patient with acute infectious hepatitis finds a low fat diet very unpalatable and continues to lose weight. Therapy should be directed mainly

TABLE I

COMPARATIVE EFFECTS OF METHIONINE, CHOLINE, LIVER EXTRACT AND SALINE ON THE AVERAGE PERIOD REQUIRED FOR RECOVERY IN PATIENTS WITH INFECTIOUS HEPATITIS

Medication	No. of Patients	Net Change in Weight in Hospital (Kg.)	Average Duration of Illness (Days)
Intravenous methionine	16	+2.9	53.5
Oral choline	29	+3.1	50.7
Intravenous crude liver extract	34	+3.5	48.9
Intravenous saline (control group)	31	+3.1	51.5

toward increasing the caloric intake as much as possible during the acute stage of the disease in order to return the patient to positive nitrogen balance and permit him to regain the initial loss in weight.

With respect to the other substances which have been advocated for the treatment of acute hepatitis, methionine, choline, liver extract, amigen, etc., no definite evidence is available that they are of value for this purpose. Table 1 illustrates the comparative duration of illness in three groups of patients with various supplements to a standard diet. The control group did just as well as the other groups given methionine, choline and liver extract.

In the severely ill or comatose patient with acute infectious hepatitis protein should be administered in the form of concentrated plasma albumin or whole plasma. Continuous infusions of glucose are necessary to provide an adequate caloric intake. Intravenous administration of amino acids proved of little value because of their rapid excretion.

When the patient has recovered from the acute stage of infectious hepatitis and his plasma bilirubin and bromsulfalein retention have fallen to normal, he should be observed very closely for the possible development of a relapse following a return to activity. This is a critical period and liver function tests should be carried out with special care. With the appearance of the slightest sign of relapse the patient should be returned to bed. The importance of such therapy has been emphasized by the severe course of the illness in certain patients who suffered relapses under wartime conditions and were forced to continue activity. The early detection and treatment of relapses is perhaps the most important aspect of the care of patients with infectious hepatitis.

The treatment of chronic hepatitis and post-hepatitis cirrhosis is a difficult problem. Once cirrhosis has become established, the disease takes a malignant course and is but little amenable to the usual dietary forms of treatment which are valuable in Laennec's cirrhosis. In an occasional patient with poor appetite the administration of intravenous liver extract has brought about improvement.

A characteristic feature of the later stages of this disease is the extreme liver damage that is present, manifesting itself in very low plasma albumin levels. The administration of concentrated human albumin is of dramatic temporary benefit in these patients. Figure 3 illustrates the course of a Navy veteran who developed severe cirrhosis following a relapse of infectious hepatitis under wartime conditions. Ascites and edema appeared and did not respond to dietary therapy. Following the administration of approximately twenty-seven 25-Gm. units of human albumin, diuresis occurred with loss of all ascites and edema. The general condition of the patient improved greatly and he led a normal life for approximately three months. Hepatic function did not improve, however, and the plasma albumin level gradually fell, resulting in further edema and ascites. This could be readily controlled by the administration of more albumin and the

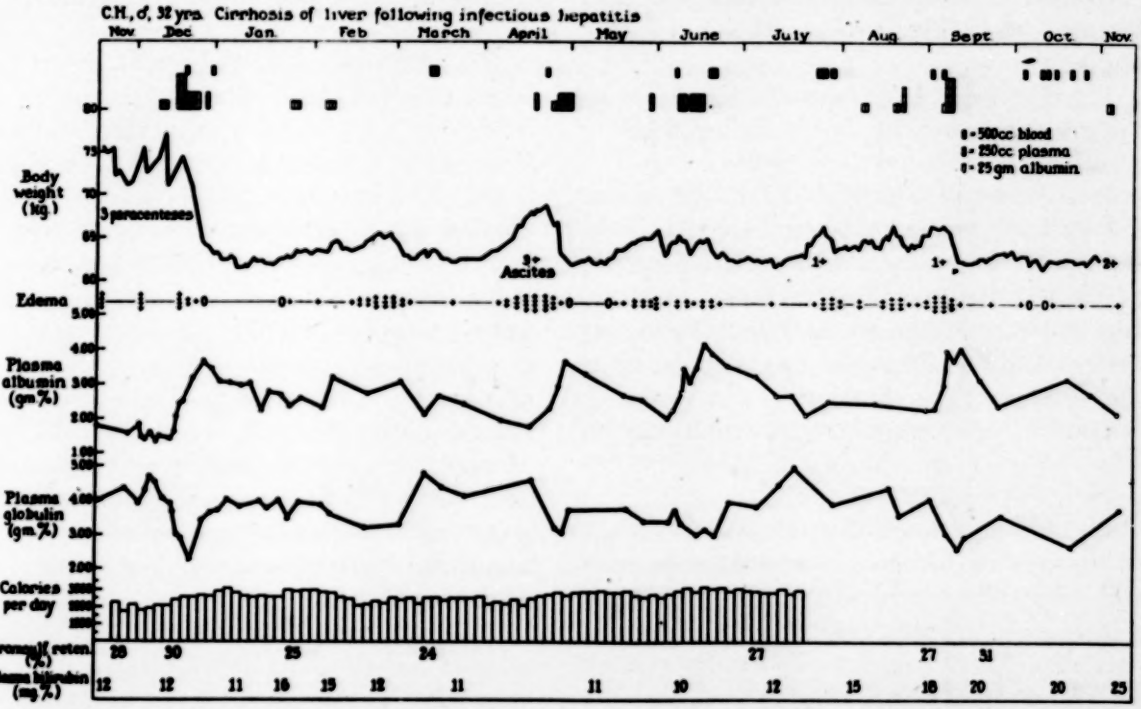
C.H., ♂, 32 yrs. Cirrhosis of liver following infectious hepatitis
Nov Dec Jan Feb March April May June July Aug Sept Oct Nov
1 = 500cc blood
1 = 250cc plasma
1 = 25 gm albumin
Body weight (kg.)
3 paracenteses
3+ Ascites
1+
1+
2+
Edema
Plasma albumin (gm%)
Plasma globulin (gm%)
Calories per day
Bromsulf reten. (%)
Plasma bilirubin (mg%)
25 30 25 24 27 27 31
12 12 11 16 19 12 11 11 10 12 15 16 20 20 25

FIG. 3. Course of a patient with cirrhosis and generalized anasarca eighteen months after infectious hepatitis showing rapid and complete loss of edema and ascites following 27 units of albumin and control of recurrent ascites with additional albumin. Death was due to uncontrollable bleeding tendency.

patient was kept virtually free of ascites for approximately one year. He finally died as a result of a marked bleeding tendency from his mucous membranes, a manifestation of severe liver damage attributable to deficient production of prothrombin and fibrinogen. However, it was believed that albumin therapy probably prolonged his life for almost a year.

DR. SIDNEY C. WERNER: Dr. Kunkel, was there a corresponding fall in globulin in the serum when you gave albumin?

DR. KUNKEL: The globulin in the serum fell initially with the albumin administration. This is purely a hemodilution effect, a result of the increase in plasma volume. Electrophoretic patterns have furnished further evidence that the fall in globulin is due solely to hemodilution.

DR. DANA W. ATCHLEY: I would like to ask how much emphasis you place on forcing carbohydrate.

DR. KUNKEL: Carbohydrate was furnished in the diet in an amount necessary to meet the caloric requirements of the individual. Additional carbohydrate was not given because this would tend to lower the protein and fat consumption.

DR. ATCHLEY: Why do you prefer to give liver intravenously? Do you not think that the same amount intramuscularly would affect the appetite to the same degree and produce an equal therapeutic effect?

DR. KUNKEL: By intravenous administration it is possible to give larger amounts of liver extract with less discomfort to the patient. These larger doses appear to increase the appetite considerably more than small intramuscular administrations.

DR. HANGER: The crude liver that you were giving was the commercial product Intraheptol?

DR. KUNKEL: Yes.

DOCTOR: What are your present views concerning intravenous liver therapy in liver disease?

DR. KUNKEL: In patients with complications following infectious hepatitis, we never found it to be of dramatic benefit; in some instances improvement in appetite and gain in weight occurred, but in no instance was there any significant change in the results of liver function tests. However, in patients with the nutritional type of cirrhosis, i.e., classic Laennec's cirrhosis, we believe liver extract is of definite value. This we believe is also due to improvement in appetite and in the general nutritional state.

DR. ATCHLEY: Nobody mentioned the important problem of alcohol. Abstinence is important during the acute stage but how long before a man becomes a citizen again?

DR. KUNKEL: We usually advise against alcohol for at least three months after an attack of infectious hepatitis. After that we leave it up to the patient himself. Intolerance to alcohol was one of the commonest complaints in patients with mild symptoms of a lingering hepatitis and as a result they stayed away from it. It appeared as if alcohol has a specific bad effect on the liver in these border line states. The patients who recovered completely tolerated alcohol without difficulty within a few weeks after an attack of hepatitis.

DR. ATCHLEY: Have you seen any specific relapse based upon overindulgence in alcohol during the convalescent period?

DR. KUNKEL: Yes, the one severe relapse of our group, with return of clinical jaundice, occurred in a patient who did considerable drinking as soon as he left the hospital.

DR. ATCHLEY: You emphasized activity entirely when you were discussing relapses. I wonder whether the amount of activity would be a factor there?

DR. KUNKEL: It was the impression that overactivity was more prone to cause relapses in the convalescent period. However, there was no doubt that even mild activity sometimes brought on a relapse.

DR. ATCHLEY: Was alcohol a factor in the people who developed a fatal cirrhosis?

DR. KUNKEL: It may have been in one case but not in the others.

DR. KENNETH B. TURNER: What is the mechanism of the relapse?

DR. KUNKEL: That is a very difficult question. Whether it results from a persistent

virus which is re-activated or whether it is purely a metabolic disturbance is not known. Dr. Neefe's experiments, we hope, will answer this important question.

STUDENT: I wonder if Dr. Neefe would like to say a word or two about the persistence of the virus in the group of patients that Dr. Kunkel has been talking about. In the type of hepatitis in which you induce the disease, Dr. Neefe, are factors other than the initiating cause responsible for persistence of the disease, or is there a persistence of the virus itself?

DR. NEEFE: Of our volunteers with induced hepatitis, several had a persistence of symptoms resulting in partial disability for a prolonged period after subsidence of acute manifestations of hepatitis, what one might call a chronic, non-icteric, active hepatitis. We collected a number of feces and serum specimens from these subjects through the period of approximately one year during which the symptoms and abnormal findings in respect to the hepatic tests continued. In addition, one subject had a liver biopsy obtained by laparotomy and a small portion of the liver specimen was frozen to be available for testing. These three materials were administered to separate groups of volunteers with the hope of determining whether or not virus was present in these materials during this period after the subsidence of the acute disease. If present, one might postulate that the virus had something to do with the persistence of the symptoms and abnormal findings. Unfortunately, the results of the experiment were not conclusive. There were five men who were given the liver biopsy material and, about twenty-eight days after inoculation, one of the men developed an acute illness characterized by marked abdominal pain, anorexia, nausea, vomiting and definite enlargement and tenderness of the liver. However, he failed to develop some of the changes that we usually find with acute hepatitis, namely, evidences of marked disturbance in liver function, and, of course, he did not develop jaundice. He did have a minor degree of bromsulfalein retention, but not more than one might see during the course of almost any acute illness. Because of the time of the onset of symptoms after inoculation and the definite enlargement and tenderness of the liver, one would certainly be inclined to call the disease hepatitis were it not for the absence of definite laboratory evidence of hepatic disturbance. Similar but less acute manifestations occurred in several of the men who received the feces but again the laboratory findings were not conclusive. Thus, we were left with a situation in which something had happened but could not be interpreted. The volunteers who received the serum were, in a sense, a fairly good control group in that they showed no abnormalities in the way of symptoms or signs. One can only say, therefore, that there was a suggestion that something was present in the materials administered that caused some sort of illness. Exactly what it was we could not determine. It is hoped that it will be possible to attempt to transfer the disease further to other volunteers by using serum and feces obtained from these men. Unfortunately, this has not been possible to date. As far as I know this is the only direct attempt to demonstrate persistence of virus in chronic cases and unfortunately it leaves us still in the dark.

SUMMARY

DR. HEATH: Infectious hepatitis has been shown in recent years to be a viral disease. For despite the fact that the virus has never been isolated or visualized, despite the fact that characteristic lesions have never been produced in the chick embryo or the virus grown in tissue culture, despite the failure to demonstrate inclusion bodies in infected material and despite the failure to find a susceptible laboratory animal, the work of Neefe and others using human volunteers has conclusively shown that an agent can be isolated from human cases of infectious hepatitis which will reproduce the disease when administered to other human beings.

This infectious agent passes bacteria-retaining filters, is not destroyed by ordinary bacterial disinfectants, survives 56°c. for one

hour and remains infectious under a wide range of conditions. On the other hand, it may be inactivated in plasma on exposure to ultraviolet light and under certain conditions may be destroyed when subjected to 60°c. for several hours.

So far, at least two distinct varieties of hepatitis-producing agents have been identified, the IH and SH strains. The former, isolated from cases of epidemic infectious hepatitis, would appear to be the more widespread and common agent. After inoculation it produces symptoms, often with fever, in twelve to forty-two days although the incidence of takes is considerably higher (80 per cent) when the material is given orally than when injected parenterally. The resulting disease cannot be distinguished either pathologically or in its clinical course from that due to SH virus, except that gamma globulin when given during the incubation period protects against or modifies the IH disease, but so far has not been shown to be active against the SH disease.

SH virus can be inoculated successfully (75 per cent) only by the parenteral route and then exhibits a prolonged incubation period of 60 to 300 days, during which time the virus is present in the blood. The thymol turbidity test may be negative in SH hepatitis.

During the period of active jaundice viremia is common to both diseases and presumably the virus may be found in the stool in each case (though demonstrated only in IH), but how long either of these phenomena persists after recovery is not known. Each virus infection is followed by the development of long-term specific immunity, presumably permanent, but there is no cross-immunity.

How infectious hepatitis is transmitted is not entirely clear. A certain number of cases due to IH virus apparently follow the ingestion of infected material. But accidental transmission of both IH and SH virus may follow upon improper handling of needles and syringes so that adequate heat sterilization of these implements and avoidance of the "multiple dose—single syringe" technic seems essential. Sterilization of feces, urine, bedside utensils, bed linen and blankets is also recommended. When these measures have been carried out, accidental transmission of either virus has not been a problem.

The hepatic lesion in virus hepatitis may have three components:

1. *Parenchymal damage* is associated with a positive cephalin flocculation test, elevation of the direct serum bilirubin and impaired liver function as measured by galactose tolerance and cholesterol esterification.

2. *Involvement of the reticuloendothelial system*, i.e., the Kupffer cells and the sinusoidal lining, leads to hyperglobulinemia and portal obstruction as evidenced by splenomegaly, ascites and elevation of indirect serum bilirubin and serum alkaline phosphatase.

3. *Periportal inflammation* may produce abnormalities of both types noted above.

Some 60 per cent of patients following recovery from acute hepatitis may have symptoms such as fatigue, drowsiness, fatty food and alcohol intolerance, in addition to physical findings such as liver tenderness, without any detectable abnormality in liver function tests. In the 15 per cent with definite relapse the laboratory findings are usually limited to bromsulfalein retention and positive flocculation tests, although in instances of severe relapse, jaundice may recur with alteration in other tests as well.

Therapy of the acute disease is limited chiefly to bed rest and dietary measures. The former should be complete and prolonged until the bromsulfalein retention is normal since too early activity may be responsible for relapse. A high caloric diet with high protein and, after the first few days of anorexia and fatty food intolerance, high fat content seems most desirable at the present time. Liver extract intravenously may stimulate the appetite, especially in chronic cases, but it should be emphasized that ordinary liver extract prepared for intramuscular injection cannot be so used. Finally, in patients with edema and ascites on the basis of hypoalbuminemia, the administration of plasma or human albumin may be temporarily beneficial.

Clinico-pathologic Conference

Recurrent Progressively Severe Headaches Leading to Coma and Death*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, E. E., (B. H. No. 141717), a forty-six year old tavern keeper, entered the Barnes Hospital on December 4, 1946, complaining of headaches. The family history was of interest only in that the patient's father had died at the age of sixty-four of Bright's disease. The past history was significant in that at the age of twenty the patient developed a chancre on the lip. A diagnosis of syphilis was made by a physician after three serologic tests had been positive. The patient was treated with six injections of "606" and by oral medication given in drop doses. Subsequently, three other serologic tests were negative. At the age of twenty-two the patient had an episode of abdominal pain and was told by a physician that he had a peptic ulcer; the diagnosis was said to have been confirmed by roentgen ray examination. The gastrointestinal symptoms recurred periodically thereafter but had been absent for three or four years prior to the patient's admission to the hospital. Otherwise, he had enjoyed good health. He was a cafe owner and had cooked and attended bar; he stated that he drank approximately 1 pint of hard liquor daily.

The patient was apparently well until three weeks before admission when a particle of food lodged in his throat. As a result, he experienced paroxysms of coughing and during one of these he developed a sudden pain behind the right eye which was described as quite severe. The pain recurred daily thereafter lasting five minutes to five hours. It was aggravated by cough and not relieved by any medication. The episodes of pain were characteristically sudden in onset and disappeared just as rapidly; they occurred chiefly during the day and rarely at night. No dizziness, faintness or other symptoms were noted until five days before entry when the headaches became associated with vomiting. Over a period of five days the patient vomited approximately twelve times. There was no accompanying nausea but a poorly defined unpleasant sensation was said to have preceded the episodes of emesis. In the three weeks during which he had symptoms the patient lost approximately 20 pounds.

At the time he entered the hospital physical examination revealed his temperature to be 36.6°C., pulse 54, respirations 16 and blood pressure 120/70. The patient was a well developed, well nourished male who lay flat in bed; he held his hand over his eyes and complained of generalized headache. He seemed depressed and gave only the briefest answers to questions. The pupils reacted sluggishly to light and accommodation but were round, regular and equal. Examination of the optic fundi showed the discs to be clearly outlined but the veins appeared full. The teeth were dirty and the breath was foul. Examination of the lungs was entirely negative. The heart was not enlarged and

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the rhythm was regular; the sounds were normal in quality and there were no murmurs. The abdomen was soft; the liver edge could be felt just at the costal margin but no other organs or masses were made out. Rectal examination revealed only minimal prostatic enlargement. Neurologic examination was essentially negative.

Laboratory data were as follows: Blood count: red cells, 5,060,000; hemoglobin, 15.2 Gm.; white cells, 8,600; differential count: eosinophiles, 1 per cent; stab forms, 15 per cent; segmented forms, 62 per cent; lymphocytes, 20 per cent and monocytes 2 per cent. Urinalysis: albumin, trace; sediment, negative. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 17 mg. per cent; blood sugar: 71 mg. per cent. Roentgenograms of the skull: indeterminate.

During his hospital stay the patient had very frequent headaches and he remained dull and depressed. Codeine and aspirin gave him little or no relief. Early in the evening of his third hospital day the patient seemed confused and his conversation was without continuity. Later that night he was found on the floor adjacent to the bed. It was not known whether he had fallen out of bed or had slipped after getting up. He was examined carefully and no evidence of injury or additional abnormal physical findings were found. Four hours later the call light outside his room went on and when the nurse arrived a few seconds later she again found the patient on the floor, this time with a small laceration over the occiput. He was again examined by a house officer and responded readily to questions but his answers were definitely confused. He rapidly became stuporous. On examination the blood pressure was 130/80 and the pulse rate 60. The eyes were turned to the left and the pupils, although small, were equal and reacted to light and accommodation. The fundi appeared as they had at the time of the original examination. The neck was not stiff. The extremities were spastic, the lower ones especially so, and bilateral pathologic toe signs and ankle clonus were elicited. The abdominal reflexes were absent.

The patient became extremely hyperactive and difficult to restrain; he was therefore given 12 cc. of paraldehyde by mouth and following administration of the drug he quieted down so that he could be controlled. During the course of the next few hours spasticity increased, particularly on the right side, and the neck was said to have become somewhat stiff. However, it could not be determined whether the stiffness was attributable to the state of generalized rigidity or due to true meningeal irritation.

Two hours later the patient's pulse rate had risen to 120. Respirations were regular, deep and stertorous. Spasticity of the extremities appeared to have decreased to some extent. The patient was seen in consultation by a neurologic surgeon and a lumbar puncture was advised. This procedure was performed with great care; the initial pressure was 350 mm. of water and the fluid appeared clear. After 2 cc. had been removed very slowly the patient stopped breathing and in spite of artificial respiration and other emergency measures he could not be revived. Subsequently, a Wassermann test on the spinal fluid was reported as negative. Death occurred on December 7, 1946.

CLINICAL DISCUSSION

DR. W. BARRY WOOD, JR.: This case presents one of the most difficult diagnostic problems that we have faced for some time in these conferences. The patient suffered primarily from a neurologic disorder and we shall rely on Dr. Jones, who saw the patient in consultation, and on Dr. Levy for aid in our attempt to reach a diagnosis. It seems advisable to divide the discussion into two parts: First, we shall try to localize the lesion in the central nervous system and secondly, we shall discuss the possible causes of the lesion. Dr. Jones, I believe you saw this patient after he had fallen out of bed on his third day in the hospital. According to the history, he was given paraldehyde shortly before the accident. From your examination at that time what was your impression as to the site of the principal lesion?

DR. ANDREW B. JONES: At that time I thought that the mid-brain and the upper pons were involved.

DR. WOOD: Could you tell us specifically the signs that you considered important?

DR. JONES: The rigidity and spasticity of the lower extremities, the bilateral pyramidal tract signs and the pathologic toe signs all seemed significant.

DR. WOOD: Could a lesion in any other part of the brain give rise to those signs, Dr. Jones?

DR. JONES: Not that I know of. I should like to qualify my statement, however, by stating that the lesion itself would not have had to be in that location but would have to be in a position to exert pressure on that portion of the brain.

DR. WOOD: May such signs be seen in subarachnoid hemorrhage if, as a result of the bleeding, there is irritation of the brain?

DR. JONES: I cannot recall that I have ever seen such a clinical picture.

DR. WOOD: What causes would you think of here, Dr. Levy, other than a lesion in the mid-brain or pons? Can we dismiss involvement of any other part of the nervous system?

DR. IRWIN LEVY: It seems to me that hemorrhage into the ventricle is a possibility. I did not see this patient but considering the signs already discussed and adding the facts that the patient was described as looking to the left, that his right side showed more involvement than the left and that he was unconscious, one would be justified in entertaining a diagnosis of interventricular hemorrhage.

DR. WOOD: Dr. Jones, would you mind describing for us again the signs as you found them?

DR. JONES: At the time that I saw the patient he was in coma and could not be roused by any stimulus. His head and eyes were turned to the left. There were very rapid movements of both eyes but occasionally one eye would deviate. The neck was not stiff but the extremities were spastic and were held rigidly in extension. There were pathologic toe signs. Occasionally, the upper extremities would relax.

DR. WOOD: Did you consider the possibility of hemorrhage into a ventricle as suggested by Dr. Levy?

DR. JONES: Yes, I thought of it but because the head and eyes were turned to one side, I thought more of a vascular lesion in the mid-brain or pons or of some lesion other than hemorrhage exerting pressure on this area. Ventricular hemorrhages may cause spasticity but as a rule the pupils are small and the signs are more equal bilaterally. The signs in this case, although they were somewhat symmetrical, were more pronounced on the right.

DR. WOOD: Dr. Levy, it is interesting that when Dr. Henry Schwartz saw this patient he made the same diagnostic suggestion that you have made, namely, hemorrhage into the ventricle. We seem then to have two possibilities—a lesion in or about the pons or a large hemorrhage into the ventricle. Have you any comments to add concerning the localization of the lesion, Dr. Charles?

DR. BEN H. CHARLES: No, there is little that I can add. When I first saw the patient, there were no localizing signs.

DR. JONES: Dr. Wood, this patient was admitted to the hospital because of headaches. In other words, he had headache before he fell and sustained his injury. When I saw him immediately after his injury, I considered the possibility of epidural or subdural hemorrhage. In the light of the history, however, the possibility of a brain tumor should also be kept in mind.

DR. WOOD: If the patient had a brain tumor, would it have had to lie in the region of the medulla or the pons?

DR. JONES: Yes, or else it would have had to be in an adjacent area so as to exert pressure in that region.

DR. WOOD: Dr. Levy, can the possibility of interventricular hemorrhage be eliminated in view of the clear spinal fluid?

DR. LEVY: While the finding of clear spinal fluid certainly constitutes evidence against ventricular hemorrhage, occasion-

ally there is a delay in the appearance of blood in the lumbar fluid. The lumbar puncture was done shortly after the accident and it is conceivable that this case represents one of those instances in which the blood had not yet reached the lumbar space.

DR. WOOD: How would you explain the headaches and vomiting which the patient had prior to entering the hospital, some three weeks before his fall?

DR. LEVY: It is recorded that the patient coughed and had sudden pain behind the right eye. If the hemorrhage had been interventricular, it would have been due to a ruptured vessel on the left, probably in the left hemisphere. The pain behind the right eye on coughing suggests a stretching effect on the large vessels at the base of the brain. The possibility of central nervous system syphilis must also be considered. I do not know the significance of the fact that his pupils were described as sluggish.

DR. JONES: I do not agree with Dr. Levy for it seems to me that the possibility of interventricular hemorrhage need not be considered further in view of the fact that blood was not found in the spinal fluid.

DR. WOOD: Dr. Turner, would you restate the sequence of events and specify the exact interval between the accident and the lumbar puncture.

DR. GLENN O. TURNER: The patient was found out of bed for the first time about 3 A.M. and the next time, some four hours later, about 7 A.M. The lumbar puncture was not done until approximately noon.

DR. LEVY: I still think that the five-hour interval between the occurrence of the second fall and the performance of the lumbar puncture does not rule out interventricular hemorrhage. I am interested in the initial pressure of 350 mm.; unless, as Dr. Jones suggests, there was a tumor, the finding of an initial spinal fluid pressure of 350 mm. is compatible with an acute accident and suggests hemorrhage.

DR. WOOD: Why should this man have had a cerebral hemorrhage? He was in his forties and apparently in good health.

DR. LEVY: In view of the fact that his blood pressure was normal, rupture of a congenital aneurysm seems the most likely cause. Syphilis must also be considered.

DR. WOOD: Dr. Scott, may we rule out syphilis on the basis of the negative spinal fluid Wassermann?

DR. VIRGIL C. SCOTT: Syphilis cannot be ruled out completely but it seems very unlikely.

DR. WOOD: Dr. Jones, would you care to make a definitive diagnosis at this time?

DR. JONES: I should like to repeat that when I first saw the patient I was asked to see him because of his fall; after I had examined him the entire history was presented to me and I learned that he had come into the hospital because of previous headaches and vomiting. Therefore, although my original impression was that he had had a vascular accident secondary to immediate trauma, the occurrence of symptoms prior to admission made such a diagnosis unsatisfactory and I believed that the patient may have had a tumor.

DR. WOOD: Will you localize the tumor for us?

DR. JONES: I do not believe that the tumor was in the pons but rather in the region adjacent to it. The signs seemed to represent so-called "neighborhood signs." The tumor was probably a large one and therefore the most likely site would be in the cerebellum. Also, there may well have been hemorrhage into the tumor.

DR. WOOD: The man's entire illness covered a period of only three weeks. What type of tumor can grow rapidly enough to give rise to the symptoms recorded and also be the site of a hemorrhage?

DR. JONES: The exact type of tumor would depend somewhat on the age of the individual.

DR. WOOD: Was this man too old for a medulloblastoma?

DR. JONES: I cannot answer your question with certainty although medulloblastomas are more common in children.

DR. LEVY: Dr. Wood, I still am unable to believe that this patient had a tumor. The

history seems to me much more in keeping with a vascular accident.

DR. JONES: I agree that the original episode which was described, that is, a paroxysm of coughing and pain behind his right eye is very suggestive of an aneurysm near the bifurcation of the internal carotid artery. I do not believe, however, that the subsequent course can be explained by that diagnosis.

DR. WOOD: We have had the benefit of the opinions of two expert neurologists and have been unable as yet to reach a definitive diagnosis. Dr. Turner, you took an active part in the care of this patient. Do you have anything to add?

DR. TURNER: I should like to reemphasize the fact, stated in the protocol, that the patient became extremely hyperactive, so much so that all available personnel could not restrain him. It was for that reason that he was given the paraldehyde and when he subsequently quieted down we were able to perform a satisfactory neurologic examination.

DR. WOOD: I should like to suggest one more possibility for discussion before Dr. Moore describes the pathologic findings. This man was an alcoholic and I believe we should therefore consider the possibility of the acute hemorrhagic encephalitis which occurs in alcoholics and which may lead to their death in a relatively short period of time. I am referring to Wernicke's syndrome. Several of the patients originally described by Wernicke died in a period of two to three weeks. The lesions are located primarily in the region incriminated by Dr. Jones, and the spinal fluid is often normal despite the fact that there may be bleeding into the brain itself. I should like to ask both Dr. Levy and Dr. Jones whether the diagnosis of Wernicke's syndrome can be ruled out with certainty.

DR. LEVY: I think the fact that the patient died suddenly after lumbar puncture is against that diagnosis and I also think the initial spinal fluid pressure was too high.

DR. JONES: I considered the possibility, particularly before the results of the lumbar puncture were known. However, the usual cranial nerve findings were not present and I also discarded the diagnosis.

DR. WOOD: Are there any other comments or suggestions?

DR. PALMER H. FUTCHER: I favor the presence of a tumor in this patient although he did not have papilledema. There apparently was a mass in the cerebellar area causing an increase in intracranial pressure. I have seen patients with metastatic carcinoma of the brain in the past who have baffled the clinicians; and although no primary site seems obvious, the possibility must still be considered. The patient had coughing paroxysms and conceivably could have had a pulmonary lesion. He also had had gastrointestinal complaints although these were so longstanding that the possibility of carcinoma of the gastrointestinal tract seems less likely.

DR. WOOD: The suggestion is a good one and certainly cannot be ruled out.

MEDICAL STUDENT: Could the cough have been a precipitating factor of hemorrhage within a tumor?

DR. LEVY: Hemorrhage in a tumor is not particularly common. I do not believe that cough is often a precipitating factor.

DR. WOOD: In summary, the diagnostic possibilities in this case include a neoplasm of the central nervous system, either in the region of the medulla or pons or in an area close enough to exert pressure on the midbrain. Dr. Levy has defended the possibility of interventricular hemorrhage on the basis of a congenital aneurysm. Wernicke's syndrome was considered and finally Dr. Futcher suggested the possibility of metastatic carcinoma from the lung.

Clinical Diagnoses: ? Neoplasms of brain in or near pons, ? primary, ? metastatic from lung; ? interventricular hemorrhage from congenital aneurysm.

PATHOLOGIC DISCUSSION

DR. JAMES G. OWEN: When the cranial cavity was opened, there was no blood either in the extradural, subdural or subarachnoid spaces. The brain when removed was found

to be of normal weight, 1,400 Gm. Step sections in the cerebral hemisphere showed slight symmetrical dilatation of the lateral and third ventricles, which contained no hemorrhage. The ependyma was pale and not discolored. The right hemisphere of the cerebellum was flat and very soft, bluish-green in color, and the folia of the right hemisphere were quite obscure. At the time the brain was removed from the cranial cavity the outer surface of the right cerebellar hemisphere shelled off and revealed a large, soft, brownish-red clot. On section of this hemisphere a large cavity was seen on the right, filled with a soft, friable blood clot and lined by a shaggy, greyish, translucent mass. In the base of this mass there was a large friable, reddish blood clot. The hemorrhage and greyish tumor tissue extended inward to obscure the dentate nucleus. The portions of the medulla and the pons in this area were distinctly distorted and were pressed downward and to the left. The fourth ventricle was slightly dilated.

The other important findings at the time of autopsy were in the lungs which were expanded and heavy, weighing 1,750 Gm. On cut section a frothy, watery, serosanguineous fluid exuded. At the apex of the left lung there was a large, flat, irregular mass which was firm, white and very tightly adherent to both the parietal and visceral fluid. The tumor formed a dense cap over the apex of the left lung, extending immediately downward to become tightly adherent to the arch of the aorta just distal to the origin of the left subclavian artery. On section the tissue was firm, white, flecked with yellow and sharply demarcated from the underlying lung tissue. There were two small tumor nodules elsewhere in the upper part of the lower lobe of the left lung. Two hilar lymph nodes on the left showed similar masses. There were no signs of ulcerations in the gastrointestinal tract.

Dr. Robert A. Moore: On the basis of the gross examination, we were able to make several diagnoses: First, we made a diagnosis of a tumor involving the pleura of the left lung, the tracheobronchial lymph nodes and the cerebellar hemisphere. There was hemorrhage into the tumor in the cerebellum of considerable size. On the basis of the gross examination the type of tumor cannot be stated with certainty although two possibilities stand out. First of all, the tumor in the lung and the tumor in the brain may have been unrelated; in other words, this patient may have had two separate tumors, the one in the cerebellum, a glioma, and the lesion in the lung being primary there. Secondly, the patient may have had a primary tumor of the lung which metastasized to the brain. If the latter postulate is correct, there are again two possibilities: one that the primary tumor arose in a bronchus at the apex of the lung, in other words, a so-called Pancoast tumor. Actually, it had not yet become a Pancoast tumor for it had not crossed the pleura and involved the structures that are typically involved in that syndrome. In other words, the tumor may have been a simple tumor of the pulmonary apex without further involvement. Also the possibility exists that the tumor was a mesothelioma primary in the pleura at the apex of the lung.

Turning to the microscopic sections for our answer Figure 1 shows a section of the pulmonary tumor and one sees that it is of an alveolar type. The next section (Fig. 2) is a higher power view showing the individual cells, the variation of the size of the cells and the amount of chromatin in the nuclei. The tumor is clearly malignant and the cells certainly remind one of epithelial cells more than any other type. Figure 3A was prepared by Dr. Owen to show a quadruple mitosis. A cell may be seen which is dividing into four parts. In Figure 3B a cell shows a triple mitosis. The finding of mitoses is characteristic of tumors and is one of the criteria for the diagnosis of malignancy. When one finds triple or quadruple mitotic division in the cells collected from pleural fluid or peritoneal fluid, a diagnosis of malignant tumor can be made; normal cells do not show such multiple mitoses. Figure 4 is a section of the tumor stained to

show reticulum. It is seen that the reticulum is associated with the connective tissue and not with the individual cells. Mesotheliomas have reticulum fibers so that this finding makes it possible for us to conclude that the patient had a carcinoma of the apex of the lung and not a mesothelioma. In Figure 5 there is a section of one of the nodules in the lung. It is seen that in places the tumor fills the alveoli and in other areas it grows directly into the tissues. There is a small amount of necrosis but necrosis is not a con-

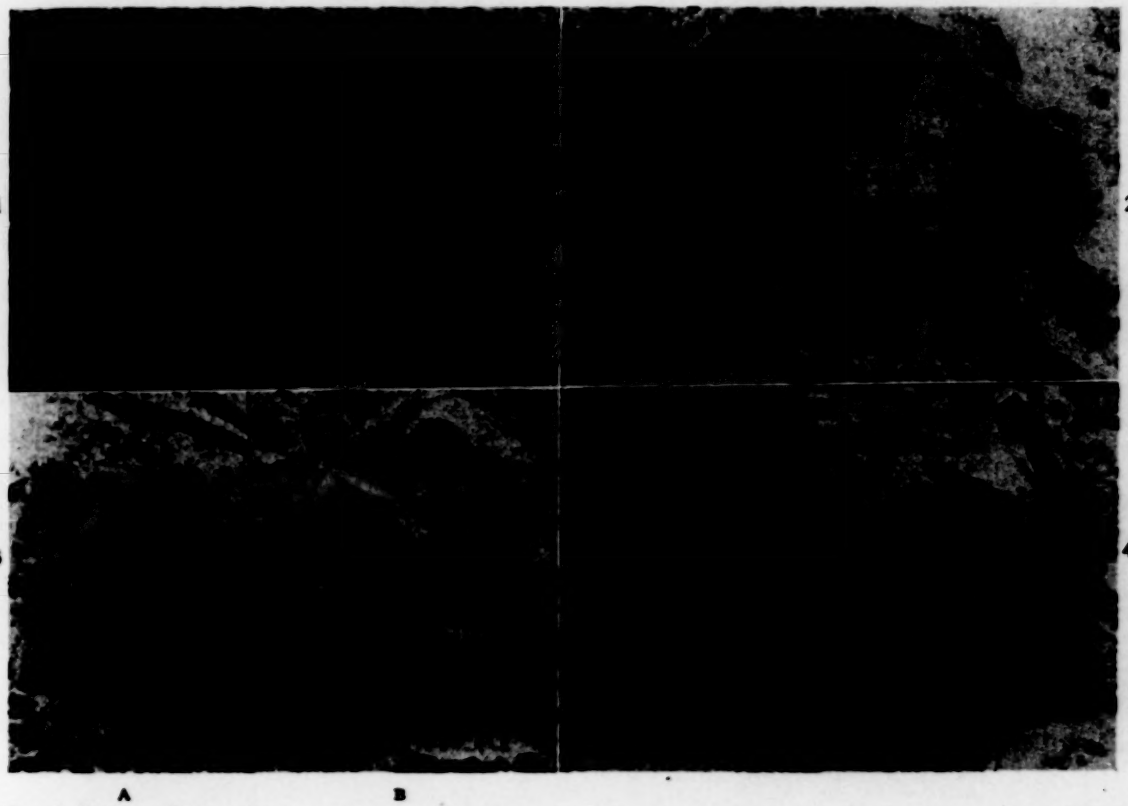

FIG. 1. Section of the pulmonary tumor.
FIG. 2. Another section from the tumor under higher magnification. The histologic appearance is characteristic of a malignant lesion.
FIG. 3. A, section from the tumor showing a quadruple mitosis; B, another area of the tumor in which a triple mitosis is visible.
FIG. 4. A section of the tumor stained to show reticulum.

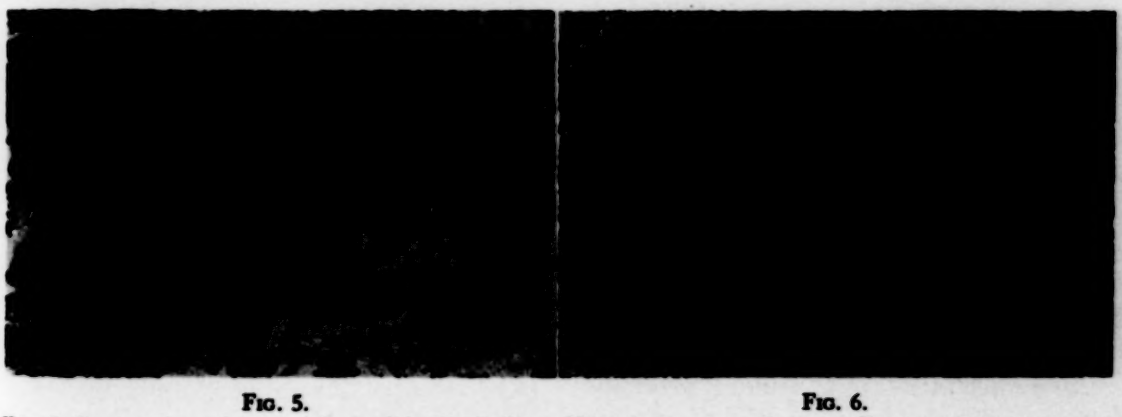

FIG. 5. FIG. 6.
FIG. 5. Section through one of the nodules in the lung. Note that some malignant cells are present within the alveoli whereas others have invaded connective tissue itself.
FIG. 6. Section of the metastatic nodule in the cerebellum.

spicuous feature of this tumor. A section through the cerebellum (Fig. 6) shows the identical cell type which allows us to conclude that the mass in the cerebellum is metastatic from the lung. It is of interest that aside from the two nodules in the lung and the nodules in the two tracheobronchial lymph nodes the cerebellar mass represented the only other metastasis. The hemorrhage into the metastatic nodule consists in most part of well preserved red blood cells. In a few areas there are granules of hemosiderin indicating hemorrhage of greater duration than a day or two.

With the anatomic evidence in relation to the clinical history the story may be completed by stating that the patient had a primary carcinoma of the apex of the lung which had metastasized to the cerebellar hemisphere. Over a period of several weeks there was an increase of intracranial pressure giving rise to the signs and symptoms which brought about his hospitalization. Somewhere between twenty-four and forty-eight hours before death, but probably at the time he fell out of bed, a large hemorrhage into the tumor occurred which led to his death. Terminally pulmonary edema occurred.

It might be well to review the diagnostic possibilities, given an undefined intracranial tumor. In a study of a large series of cases it was found that 48 per cent were gliomas, 15 per cent meningeal tumors and 18 per cent metastatic tumors. Seventy-eight to 92 per cent of a series of 114 cases of metastatic brain tumor were not clinically evident. In other words, a diagnosis of a brain tumor was not apparent on the basis of the clinical history and the physical findings. Statistically, in the patient under discussion today there was an 82 per cent chance that the clinical diagnosis would not be sufficiently apparent to allow the neurologists and internists to make a complete diagnosis. These statements are based on the experience of Baker at Duke University Hospital in North Carolina. It is of interest to consider further that of primary tumors of the lung, 15 per cent metastasize to the brain, whereas 16 per cent of primary breast tumors and 4 per cent of primary prostatic and gastric carcinomas metastasize to the brain. In other words, given a metastatic tumor in the brain the most likely primary site is the breast or the lung. In one study of a series of cases of metastatic tumor in the brain, the primary site was in the lung in 21 per cent, in the breast in 21 per cent, in the gastrointestinal tract in 11 per cent and in the prostate in 1 per cent. In contrast with these figures, the primary site of the tumor when there is no metastasis in the brain is quite different: 7 per cent in the lung, 18 per cent in the breast, 53 per cent in the gastrointestinal tract and 8 per cent in the prostate.

DR. WOOD: I would like to ask Dr. Levy if he believes that every patient who has a brain tumor and is to be operated on should have a chest film?

DR. LEVY: It certainly should be routine.

DR. WOOD: Dr. Jones, what is the explanation for the high spinal fluid pressure?

DR. JONES: It was probably due to the recent hemorrhage into the tumor.

DR. WOOD: Dr. Futcher should certainly be congratulated on suggesting the correct diagnosis.

Final Anatomic Diagnosis: Carcinoma involving the apical pleurae of the left lung, metastases to the left lung, the bronchopulmonary lymph nodes and parietal pleura on the left, and to the right cerebellar hemisphere; hemorrhage into the right cerebellar hemisphere with encephalomalacia, advanced; cerebellar pressure cone; congestion and edema of the lungs, moderate.

Negative Diagnoses: No histologic changes in the motor area of the brain of the type seen in paresis, no ulcer or scar in stomach or duodenum.

Acknowledgment: Illustrations are from the Department of Illustration, Washington University School of Medicine.

Case Report

Agranulocytosis in Induced Tertian Malaria*

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On infrequent occasions in the management of a large number of individuals undergoing artificially induced malaria, a profound depression of the granulocytes, in addition to the commonly seen leukopenia, may be encountered. Moore[7] found three cases of agranulocytosis in 600 patients treated with induced malaria. Meyer,[6] Jacobson and Abel[5] and Heldt and Goder[4] have described five similar cases, two with fatal outcome.

It is of importance that in one of the fatal cases,[6] the agranulocytosis (white blood count, 2,500, 7 per cent granulocytes) with ulceration of the tongue was noted after the sixth tertian malarial paroxysm but the malaria was not interrupted. Although the exact number of chills that were allowed subsequently was not clearly stated, the blood picture remained essentially unchanged for the ensuing seven days. On the seventh, ninth and eleventh days following the discovery of agranulocytosis blood transfusions were given. The patient died the following day of pulmonary gangrene and bullous dermatitis. Permission for necropsy was not obtained. In the other fatal case[4] agranulocytosis developed some time between the fifteenth and seventeenth tertian febrile responses. Within twenty-four hours after the seventeenth chill the patient died of pulmonary embarrassment. The outstanding finding at autopsy was a heavy, non-crepitant, dark purple lower lobe of the right lung, which on section, exuded a large amount of reddish fluid. Microscopic examination revealed "large areas of massive hemorrhage containing almost pure red cells with practically no leukocytic infiltration." In other areas the alveoli were filled with pink fluid. The anatomic diagnosis was general paresis; lobar pneumonia, right lower lobe; old subdural hematoma; splenomegaly; hepatomegaly and hemangioma of the liver.

In none of the papers was an examination of the sternal marrow or postmortem section of the bone marrow mentioned.

In slightly over one hundred military personnel treated with artificially induced tertian or quartan malaria by one of the authors (Dr. Kroll) one instance of agranulocytosis was encountered. It was deemed of interest to present the data in our case, including a report of sternal puncture study. It should be pointed out that the granulocytopenia developed during malaria therapy with no other known granulocytotoxic agent involved.

CASE REPORT

A twenty-eight year old white soldier was admitted March 2, 1945, for evaluation and treatment of neurosyphilis.

The family history and past history were not relevant. The patient denied knowledge of early acquired syphilis. His syphilitic infection was discovered in 1938, when a routine premarital serologic test for syphilis was positive. From 1938 to February, 1943, the patient received approximately fifty arm and fifty hip injections with intervening rest periods. There were no reactions to treatment. In December, 1944, routine blood Kahn and Wassermann tests were positive. The spinal fluid examination in

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December, 1944 revealed 106 white blood cells, positive globulin, Wassermann test positive in 0.1 cc., 0.25 cc., 0.5 cc., 1.0 cc. and a colloidal gold curve of 5554432111.

On admission to this army hospital the patient had no complaints. Symptomologic review of all systems was negative.

The physical examination revealed a medium built, well nourished male, 5 feet 7 inches, weighing 155 pounds. The patient was not acutely ill or in any physical distress. Mental response and orientation in all spheres were within normal limits. The abnormal findings were as follows: The right pupil was slightly larger than the left, there was a scar over the urethral meatus and moderate enlargement of postauricular lymph nodes. Aside from the minimal anisocoria there was no clinical evidence of central nervous system disease. Blood pressure was 116/84 and the pulse was 74.

The laboratory data showed that the urinalysis was normal; blood Kahn and Wassermann tests positive; NPN 28 mg. per cent; blood sugar 90 mg. per cent; icterus index 9; *x*-ray of heart and lungs and ECG normal. Smears for plasmodia were negative. Spinal fluid examination on March 5, 1945, revealed 196 white blood cells, negative globulin, total protein 20 mg. per cent, Wassermann test anticomplementary in all dilutions and a colloidal gold curve of 554321-0000. A repeat spinal fluid study on March 14, 1945, revealed 61 white blood cells, positive globulin, total protein 16 mg. per cent, Wassermann test anticomplementary in all dilutions and a colloidal gold curve of 5543322100. A complete blood count on March 3, 1945, showed 14.5 Gm. of hemoglobin (Sahli), white blood cells 12,100, 68 per cent segmented forms, 5 per cent stab forms, 2 per cent eosinophiles, 2 per cent monocytes and 23 per cent lymphocytes.

TABLE I

Date	White Blood Cells	Segmented Forms, Per Cent	Juvenile Forms, Per Cent	Stab Forms, Per Cent	Basophiles, Per Cent	Eosinophiles, Per Cent	Monocytes, Per Cent	Lymphocytes, Per Cent
March 29	3,800	9		7			6	78
March 30	3,450	3		1	3		5	88
March 31	4,750	6		1	1		2	91
April 1	4,300	3		2	2		5	89
April 2	4,850	10	2	6		1	4	76
April 4	4,300	20		2			1	76
April 5	5,250	38		2	1	1	3	57
April 6	6,600	32		5		1	3	58
April 7	10,400	41		3			3	52
April 9	7,750	37					3	60
April 12	8,250	34		7		1	2	56
April 16	10,450	50		1		4	1	44
April 23	8,550	40		4		4	2	50

During the clinical course a diagnosis of asymptomatic neurosyphilis (Grade III) was made. On March 15, 1945, the patient was inoculated intravenously with 4 cc. of tertian malarial blood. The initial febrile paroxysm occurred on March 17, 1945; thereafter, chills recurred regularly at thirty-three to thirty-six hour intervals. Blood smears revealed P. vivax. The white blood count on March 19, 1945, was 7,600, with 58 per cent segmented forms, 2 per cent stab forms, 2 per cent monocytes and 38 per cent lymphocytes. Except for marked weakness, which was not considered unusual, the patient tolerated malaria therapy well. Routine blood counts, performed twice weekly, were within expected limits until March 29, 1945, when at the ninth febrile paroxysm, a precipitous drop in granulocytes was observed. Simultaneously, for the first time slight enlargement of the spleen was detected. A white blood count the next day disclosed a further decline in granulocytes and antimalarial therapy, consisting of 0.2 Gm. of atabrine every six hours for five doses followed by 0.1 Gm. of the drug three times a day for six days, was promptly instituted. Despite the

atabrine barrier the patient broke through on March 31, 1945, with another febrile paroxysm (the tenth). Table 1 demonstrates the serial white blood counts.

On April 1, 1945, the patient complained of a cold, manifested by nasal discharge and dry cough. The physical examination revealed no abnormality of the respiratory tract except a slight redness of the pharynx. As a prophylactic measure, 25,000 units of penicillin were administered intramuscularly every three hours for a total of 850,000 units. The symptoms of upper respiratory infection subsided in a few days and the patient enjoyed an uneventful convalescence from malaria. Mapharsen therapy consisting of 0.06 Gm. twice weekly was instituted five weeks following cessation of malaria. After eight injections of the arsenical, which was tolerated without any untoward clinical or hematologic reaction, the patient was discharged from the hospital.

A specimen of the sternal marrow taken on March 31, 1945, revealed a marrow of normal cellularity. The count of 1,000 marrow cells was as follows: Myeloblasts 2.0 per cent; promyelocytes 4.0 per cent; myelocytes, neutrophilic 33.5 per cent; metamyelocytes, eosinophilic 0.5 per cent; metamyelocytes, neutrophilic 18.5 per cent; neutrophiles 3.5 per cent; lymphocytes 10.0 per cent; erythrogones 0.0 per cent; normoblasts A, 1.0 per cent; normoblasts B, 12.0 per cent; normoblasts C, 9.0 per cent; plasma cells 2.0 per cent and distorted cells 4.0 per cent. Many of the metamyelocytes had poorly differentiated granules. Vacuoles were noted in the cytoplasm and in the nucleus of a number of the myelocytes. Erythropoiesis was normal and an ample number of megakaryocytes were present.

COMMENTS

The question may be raised as to whether the blood picture in this patient represents the leukopenia which commonly accompanies malaria or whether it represents a true agranulocytosis. In our experience with a large number of soldiers suffering from malaria, incurred in both the Mediterranean and Southwest Pacific Theaters of Operation, and with patients subjected to induced malaria we have not encountered granulocytopenia approaching this magnitude. In addition, the sternal marrow aspiration revealed myeloid cells in normal abundance although mature granulocytes were markedly reduced. This bone marrow picture was found in agranulocytosis by FitzHugh and Krumbhaar[2] who have interpreted it as a maturation arrest. Moreover, the fatal outcome in the two reported patients indicates that the depression of granulocytes does reach dangerously low levels. The absence of granulocytes in the pneumonic infiltration in one of the reported fatal cases is supporting evidence that this condition is a true agranulocytosis rather than the usual leukopenia of malaria. A similar clinical picture has been observed in kala-azar by Zia and Forkner[10] who also considered that this was "not merely an exaggeration of the usual leukopenia."

The mechanism of the production of this condition is obscure in our patient. In several previously reported cases the issue was complicated by the administration of drugs prior to discovery of the blood picture; however, in others no drugs were administered and none were administered to our patient. It appears reasonable to presume that malaria is capable of acting on the bone marrow to produce an alarming paucity of peripheral granulocytes. This deleterious effect may occur late in the course of induced malaria, as in our patient, or early as described by Jacobson and Abel.[5]

The case of agranulocytosis reported by Franks and Davis[3] may possibly represent agranulocytosis occurring after the second malarial paroxysm. These authors attributed the agranulocytosis to quinine, because of an increase in the percentage of granulocytes after discontinuing the medication. However, scrutiny of their data revealed that although the percentage of granulocytes did not increase until quinine was